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Prefrontal white matter volume is disproportionately larger in humans than in other primates

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Determining how the human brain differs from nonhuman primate brains is central to understanding human behavioral evolution. There is currently dispute over whether the prefrontal cortex, which mediates evolutionarily interesting behaviors, has increased disproportionately. Using magnetic resonance imaging brain scans from 11 primate species, we measured gray, white and total volumes for both prefrontal and the entire cerebrum on each specimen ($n = 46$). In relative terms, prefrontal white matter shows the largest difference between human and nonhuman, whereas gray matter shows no significant difference. This suggests that connectional elaboration (as gauged by white matter volume) played a key role in human brain evolution.

Although the human brain is around three times larger than expected for a primate of our body size, it does not seem to be simply a scaled-up version of a primate brain[1]. Because neural tissue is evolutionarily expensive (for metabolic[2] and maturational[3] reasons), changes in relative proportions in different parts of the brain are likely to be behaviorally adaptive. Thus, determining the various ways in which the human brain is different from nonhuman primate brains is of central importance to understanding human evolution. It is clear that at least some areas of the human brain are proportionately smaller than predicted based on primate scaling trends. For example, the human olfactory bulb is only ~30% as large and Brodmann's area 17 (primary visual cortex) only ~60% as large as predicted for a primate brain our size[4,5]. Given that the entire human brain is much larger than predicted overall, at least some areas must therefore be significantly larger than predicted.

One area of particular interest for human evolution is the prefrontal cortex, which mediates such important behaviors as planning[6], working memory[7] and memory for serial order and temporal information[8], aspects of language (Broca's area and symbolic behavior[1,9,10]), attention[11] and social information processing[12]. To the extent that the human prefrontal cortex is disproportionately large, it would suggest that some combination of these behavioral dimensions were particularly important to our evolutionary history.

Comparative studies of the entire frontal cortex (of which the prefrontal cortex is a subcomponent) have not reported disproportionate increases[13–16]. However, because some data suggest that portions of the human frontal cortex are smaller than primate data predict, other portions must necessarily be larger. A cytoarchitectural study of seven primate genera (*Homo*, *Pan*, *Pongo*, *Hylobates*, *Papio*, *Cercopithecus*, *Callithrix*)[17] has suggested that primary motor and premotor areas of the frontal cortex (Brodmann's areas 4 and 6, respectively) occupy a much smaller proportion of the cortex in humans than in primates[1]. However, a magnetic resonance imaging (MRI) study of the relative size of the precentral gyrus in humans compared to five hominoid species (*Pan paniscus*, *Pan troglodytes*, *Pongo pygmaeus*, *Gorilla gorilla*, *Hylobates lar*) reported no significant difference[15]. Because the precentral gyrus includes most of area 4 but only a portion of area 6 (ref. 18), these studies are not necessarily contradictory.

Comparative studies focusing specifically on the prefrontal cortex itself have come to conflicting conclusions regarding its relative size in humans: some suggest substantial disproportionate increases[17,19–22], whereas others suggest much more moderate increases, if any[23,24]. Methodological differences may explain these disagreements. Many have focused on cortical gray matter exclusively, using cytoarchitectural criteria to define areas[17,19,21,25], sometimes also incorporating thalamic projection patterns[24]. Only one study has used MRI to estimate the volume of the prefrontal cortex itself, though the analysis was limited to female specimens of just two species: *Homo sapiens* and *Papio cynocephalus*, thereby precluding allometric analysis[23]. Other studies have used indices of the gyrification (degree of folding) of the cortex, measured on coronal sections, as a proxy for cortical surface area[20,22]. These studies have suggested disproportionate prefrontal increases.

One component that has not been reported in previous comparative studies is the volume of white matter underlying prefrontal areas. This is potentially of great interest, because the executive role played by the prefrontal cortex depends critically on its connections to posterior processing regions. The prefrontal is known to have extensive reciprocal connections with the diencephalon, mesencephalon and limbic system, as well as numerous cortical areas that mediate higher sensory functions[26]. Overall, cortical white matter increases disproportionately with increasing brain size across mammals, though apparently not enough to maintain equal degrees of connectivity between existing regions[27]. Thus, quantifying white matter in prefrontal areas is an important goal.

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Because it is difficult to delimit the prefrontal cortex unambiguously using gross sulcal landmarks, it has been argued that definitive comparative quantitative analysis will require extensive detailed cytoarchitectural studies that, because of their expense, are not likely to be carried out in the near future[15]. However, a reasonable proxy for the prefrontal cortex can be defined as all portions of the frontal cortex anterior to the genu of the corpus callosum, in a plane perpendicular to the line connecting the anterior and posterior commissures. A consideration of primate cytoarchitectural maps[19] indicates that this method will actually underestimate human prefrontal size relative to that of other primates. Human cytoarchitectural maps (for example, Figures 49 and 50 of ref. 19) suggest that a substantial amount of prefrontal cortex extends

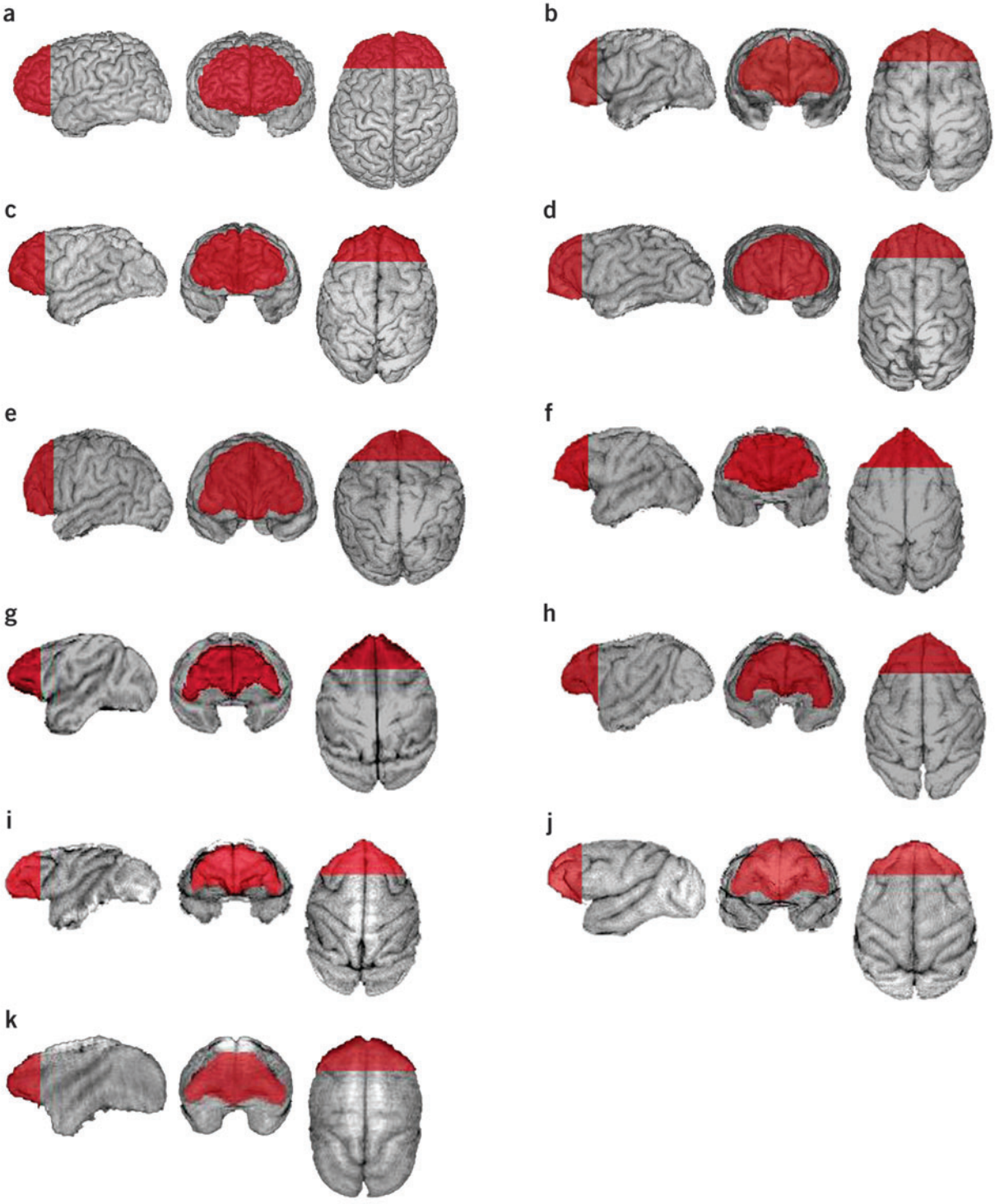


Figure 1 Three-dimensional renderings, from left lateral, anterior, and superior views (in correct left-right orientation as shown), indicating the cortical portions designated prefrontal in this study for a representative of each species. Images have been rescaled to approximately the same size for comparison. (**a**) *Homo sapiens*. (**b**) *Pan paniscus*. (**c**) *Pan troglodytes*. (**d**) *Gorilla gorilla*. (**e**) *Pongo pygmaeus*. (**f**) *Hylobates lar*. (**g**) *Cercocebus torquatus atys*. (**h**) *Papio cynocephalus*. (**i**) *Macaca mulatta*. (**j**) *Cebus apella*. (**k**) *Saimiri sciureus*.

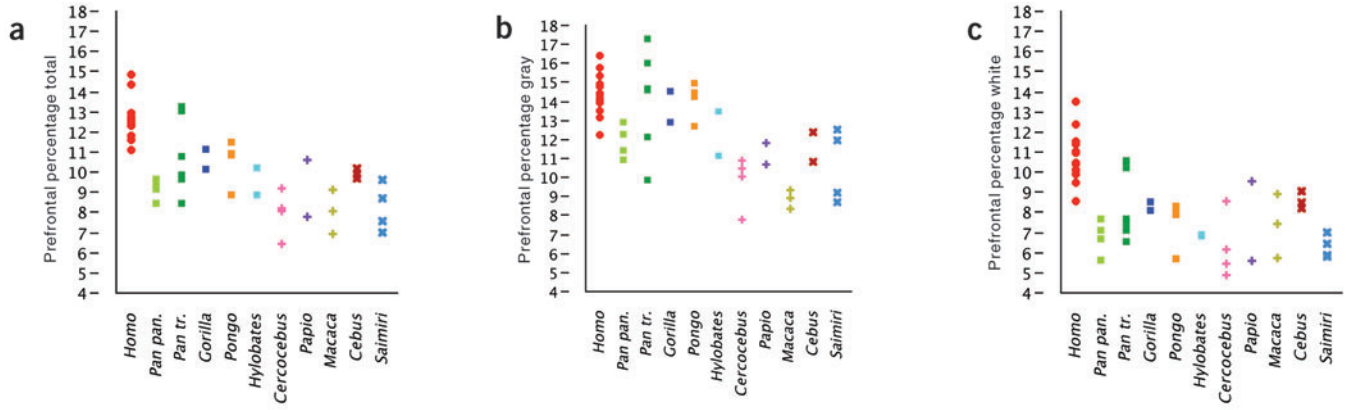


Figure 2 Percentage of cerebral volume that is prefrontal for individual specimens in 11 primate species. (**a**) Total (gray plus white) volume. (**b**) Gray volume. (**c**) White volume.

further posterior than the most anterior point of the corpus callosum, whereas nonhuman primate maps (for example, of gibbon (*Hylobates lar*) in Figures 44 and 45 and marmoset (*Hapale jacchus*) in Figures 33 and 34 of ref. 19) suggest that this method overestimates prefrontal cortex superiorly and underestimates prefrontal cortex inferiorly to approximately the same extent. Thus, defining prefrontal cortex in this way will result in a conservative estimate of any differences between humans and nonhuman primates that might be found. Furthermore, this method benefits from the fact that it can be objectively applied to MRI scans of different species, which avoids problems of postmortem tissue shrinkage found in cytoarchitectural studies of cadaver specimens[15,16,22]. MRI scans also have excellent gray-white differentiation, allowing for the measurement of white matter volumes, and also allow for the estimation of volume using standard stereological techniques[28].

Using these criteria, gray matter, white matter, and total volumes for both prefrontal and total cortex were measured on 46 high-resolution MRI scans of individuals from 11 primate species: 12 *Homo sapiens* (6 male (M), 6 female (F)), 4 *Pan paniscus* (3 M, 1 F), 6 *Pan troglodytes* (3 M, 3 F), 2 *Gorilla gorilla* (1 M, 1 F), 4 *Pongo pygmaeus* (3 M, 1 F), 2 *Hylobates lar* (1 M, 1 F), 4 *Cercocebus torquatus atys* (3 M, 1 F), 2 *Papio cynocephalus* (2 M), 3 *Macaca mulatta* (3 M), 3 *Cebus apella* (2 M, 1 F) and 4 *Saimiri sciureus* (3 M, 1 F). **Figure 1** shows the regions designated prefrontal using these criteria on three-dimensional renderings of a sample specimen from each of the species used in the present study. The effect of species differences in voxel size, ratio of females to males and subtle differences in image quality were assessed and shown to be unlikely to affect the conclusions about humans and nonhuman primates presented here (see Methods).

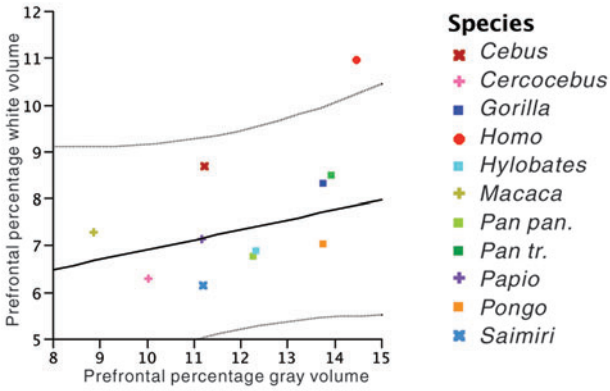
In this dataset the amount of human prefrontal cerebral volume anterior to the corpus callosum is disproportionately large on average, with the greatest human–nonhuman difference evident for the proportion of white matter that is prefrontal ('prefrontal percentage white'). Though humans do not seem to differ substantially from other hominoids in the proportion of gray matter that is prefrontal ('prefrontal percentage gray'), hominoids as a group differ significantly from nonhominoid primates (which were all monkey species in the present study). Although positive allometry is evident, average prefrontal white matter volume in humans nevertheless slightly but significantly exceeds the volume predicted from primate trends based on the size of non-prefrontal cerebral white matter volume. The absolute amounts of extra volume predicted by our analysis are substantial, being close to the size of an entire chimpanzee prefrontal cortex for total (gray plus white) and white matter volume measures.

RESULTS

Prefrontal percentages

We measured total, gray and white volumes of both prefrontal and total cerebral portions for all specimens (**Table 1**). We calculated the proportion of total cerebrum that was prefrontal (prefrontal percentage) for gray, white and total (gray plus white) volumes (data for each species are shown in **Table 2** and data from individual specimens is shown in **Fig. 2**). Average percentages were larger in *Homo sapiens* than all other primate species for each prefrontal measurement, consistent with a subjective assessment of the individual images (from **Fig. 1**). An ANOVA using Dunnett's method with *Homo sapiens* as the control group showed that human percentage prefrontal was significantly larger than for all except *Gorilla gorilla* ($P = 0.25$) for total cerebral volume. The effect seems to be almost entirely due to white matter: prefrontal percentage white in *Homo sapiens* was significantly different from all species except *Gorilla gorilla* ($P = 0.14$) and *Cebus apella* ($P = 0.11$), whereas prefrontal percentage gray differed significantly only from *Macaca mulatta*, *Cercocebus torquatus atys*, *Cebus apella* and *Saimiri sciureus*. The lack of statistically significant

Figure 3 Relationship between the proportion of total white matter volume anterior to the corpus callosum (prefrontal percentage white) compared with proportion of total gray matter anterior to the corpus callosum (prefrontal percentage gray). The solid line represents least-squares regression based on nonhuman species average values (prefrontal percentage white volume = 4.794 + 0.212 (prefrontal percentage gray volume)) and the dotted lines represent the 95% confidence intervals.



differences between *Homo sapiens* and *Gorilla gorilla* may partly be due to the fact that only two *Gorilla* brains were available. When nonhuman primate individuals were pooled into the taxonomic categories of Hominoidea (apes: *Pan Paniscus*, *Pan troglodytes*, *Gorilla gorilla*, *Pongo pygmaeus*, *Hylobates lar*), Cercopithecoidea (Old World Monkeys: *Cercocebus turquatus atys*, *Papio cynocephalus*, *Macaca mulatta*) and Platyrrhini (New World Monkeys: *Cebus apella*, *Saimiri sciureus*), *Homo sapiens* was significantly different from these groups in prefrontal percentage total cerebrum and prefrontal percentage white (ANOVA, Dunnett's method with *Homo sapiens* as control, $P < 0.0001$ for all comparisons). Although *Homo sapiens* did not differ significantly from the other hominoid genera for prefrontal percentage gray, both of these groups differed significantly from cercopithecoids and platyrrhines on this measure (ANOVA with Tukey-Kramer HSD).

These differences in prefrontal percentage translated into large absolute differences. Using the average pongid proportions (**Table 2**) to calculate predicted absolute values for the different components in humans, *Homo sapiens* had 25.7 ml (23.6%) more prefrontal total volume, 5.3 ml (7.3%) more gray matter and 17.0 ml (42.5%) more white matter than would be expected for a pongid brain of its size (ignoring allometric considerations—which are discussed below—for the moment). To put these values into perspective, we note that the entire estimated prefrontal cortex for *Pan paniscus* averaged 25.4 ml total volume, 15.4 ml gray matter and 10.0 ml white matter (**Table 1**). Although the gray volume difference was relatively small, using published neuronal density values for area 10 of the prefrontal cortex in humans[21], the extra prefrontal gray matter in humans suggests an additional ~180 million neurons beyond that predicted by cortical size difference alone.

Another way to assess these differences is to compare how much larger human values are from *Pan* species for prefrontal compared to non-prefrontal portions. The total non-prefrontal cerebral volume in humans averaged 3.7 times larger than the average of *Pan paniscus* and *Pan troglodytes*, but the prefrontal portion averaged 4.9 times larger. The pattern for gray and white volumes was consistent with the general findings above: non-prefrontal gray volume was 4.2 times larger in humans, and the prefrontal portion was 4.8 times larger; yet non-prefrontal white volume was 3.3 times larger, whereas the prefrontal portion was 5.0 times larger. As delineated in this study, white and gray matter volume differences were not distributed equally in prefrontal compared with non-prefrontal regions.

Table 1 Total, gray and white volumes of both prefrontal and total cerebral portions for all specimens studied

Species/individual specimen identifiers (sex)	Whole cerebral volume (mm^3)			Prefrontal cerebral volume (mm^3)		
	Total	Gray	White	Total	Gray	White
Homo sapiens						
7830 (M)	1,206,129	535,956	670,174	156,443	82,346	74,097
7897 (M)	1,014,949	479,788	535,161	151,317	78,913	72,404
7933 (M)	1,157,341	539,275	618,066	145,393	80,649	64,744
7972 (M)	1,085,317	501,414	583,903	141,237	74,359	66,878
8201 (M)	1,185,223	551,192	634,031	151,090	77,917	73,174
8574 (M)	1,018,913	436,578	582,335	121,015	53,490	67,525
r16 (F)	999,296	537,146	462,150	116,587	72,744	43,843
r27 (F)	915,355	518,469	396,885	102,242	68,217	34,025
r30 (F)	1,187,709	698,689	489,020	149,914	98,880	51,033
r62 (F)	840,174	476,431	363,744	104,516	68,422	36,094
r64 (F)	1,038,834	581,307	457,527	127,895	81,350	46,546
r85 (F)	1,009,091	588,281	420,810	144,950	92,849	52,101
Average[a]	1,054,861	537,044	517,817	134,383	77,511	56,872
Pan paniscus						
Bo (M)	240,699	108,102	132,597	22,014	11,806	10,207
Brian (M)	261,576	125,128	136,448	22,027	14,339	7,688
Lorel (M)	384,535	163,587	220,948	35,759	20,098	15,660
Jill (F)	250,071	118,666	131,405	24,149	15,349	8,800
Average[a]	272,837	125,469	147,368	25,374	15,382	9,993
Pan troglodytes						
Merv (M)	334,724	135,354	199,370	44,385	23,368	21,017
Laz (M)	237,988	111,072	126,917	20,878	10,540	10,338
Jimmy Carter (M)	263,789	130,447	133,343	28,507	19,051	9,456
Mary (F)	271,766	112,168	159,599	23,006	11,087	11,919
Lulu (F)	248,056	102,013	146,042	24,556	14,966	9,590
Kengee (F)	310,735	152,098	158,638	40,613	24,389	16,223
Average[a]	277,843	123,858	153,985	30,324	17,234	13,091
Gorilla gorilla						
Kekla (M)	377,732	165,004	212,728	38,470	21,297	17,173
Kinyani (F)	401,630	176,006	225,624	44,839	25,542	19,297
Average[a]	389,681	170,505	219,176	41,655	23,419	18,235
Pongo pygmaeus						
Mentubar (M)	339,266	162,421	176,845	39,067	24,338	14,728
Minyak (M)	365,674	164,367	201,308	39,930	23,791	16,139
Molek (M)	424,841	199,384	225,457	46,176	28,429	17,747
Hati (F)	289,556	133,196	156,360	25,802	16,866	8,936
Average[a]	333,075	154,293	178,781	33,763	21,193	12,570
Hylobates lar						
Buddy (M)	66,450	31,796	34,654	5,908	3,537	2,371
Cleo (F)	65,426	33,040	32,386	6,696	4,452	2,244
Average[a]	65,938	32,418	33,520	6,302	3,994	2,307
Cercocebus turquatus atys						
FSO (M)	77,990	41,589	36,401	6,267	4,503	1,764
FWJ (M)	87,131	37,113	50,018	5,604	2,887	2,716
FYF (M)	85,664	36,106	49,558	7,841	3,623	4,218
FFK (F)	81,394	37,701	43,694	6,627	3,937	2,689
Average[a]	82,495	37,985	44,510	6,599	3,804	2,794

(continued)

Table 1 Total, gray and white volumes of both prefrontal and total cerebral portions for all specimens studied (continued)

Species/individual specimen identifiers (sex)	Whole cerebral volume (mm^3)			Prefrontal cerebral volume (mm^3)		
	Total	Gray	White	Total	Gray	White
Papio cynocephalus						
Boon1 (M)	108,135	50,685	57,450	11,427	5,962	5,466
Boon2 (M)	153,065	66,546	86,519	11,892	7,098	4,794
Average	130,600	58,615	71,985	11,660	6,530	5,130
Macaca mulatta						
153C (M)	63,202	28,771	34,430	5,094	2,555	2,540
Reg3 (M)	71,028	33,323	37,705	6,460	3,103	3,357
Rue-1 (M)	75,395	33,430	41,965	5,183	2,781	2,402
Average	69,875	31,841	38,034	5,579	2,813	2,766
Cebus apella						
Andy (M)	63,315	27,982	35,333	6,474	3,464	3,009
Vincent (M)	66,571	37,495	29,075	6,474	4,068	2,406
Binkey (F)	52,219	25,977	26,242	5,196	2,820	2,377
Average[a]	58,581	29,358	29,223	5,835	3,293	2,542
Saimiri sciureus						
S104 (M)	20,191	8,548	11,644	1,424	748	677
S105 (M)	21,818	9,069	12,750	1,665	837	828
Squirrel1 (M)	22,279	10,551	11,728	2,152	1,326	826
Squirrel2 (F)	21,654	10,181	11,472	1,894	1,217	677
Average[a]	21,542	9,785	11,756	1,820	1,094	727

[a]Average of male and female means.

Overall, the data presented here suggest that gray and white matter proportions are not tightly constrained by each other over evolutionary time. The association between prefrontal percentage white and prefrontal percentage gray was very weak: $r^2 = 0.16$ (**Fig. 3**; adjusted $r^2 = 0.05$, $n = 10$ nonhuman primate species averages, $P > 0.25$). Nevertheless, the human prefrontal percentage white value still fell outside the 95% confidence intervals for predicting prefrontal percentage white from prefrontal percentage gray, an additional indication that human prefrontal white is disproportionately large.

Prefrontal scaling relationships

If prefrontal values showed positive allometry, the relatively high human proportion might nevertheless be expected because of the large overall size of the human brain (this says nothing, however, about the possible behavioral relevance of any difference; see below). Positive allometry has been shown for the frontal cortex as a whole[16] as well as for Brodmann's area 10 within the prefrontal[21,29]. Plots of the relationships between prefrontal measures against corresponding non-prefrontal measures are shown in **Figure 4** (all values log-transformed). The lines represent least-squares regressions calculated on the nonhuman species averages (of male and female means), although individual values are plotted to allow qualitative assessment of the spread within species. All of the regressions had slopes greater than 1, though these were significant only for total volume and gray volume. (One-tailed probabilities: total volume, $P = 0.02$; gray volume, $P = 0.02$; white volume, $P = 0.12$. Including *Homo sapiens* in the calculations made all slopes significantly greater than 1.) This suggests positive allometry for prefrontal cerebral volume anterior to the corpus callosum in primates.

The average human values fell above the regression line for total volume and white matter volume but not for gray matter volume. Using these regressions, human total prefrontal volume averaged 20.7 ml (18%) larger, gray matter averaged 2.1 ml (3%) smaller, and white matter averaged 16.5 ml (41%) larger than predicted. Note that these estimates are very close to those obtained above simply using average pongid prefrontal percentage value for white volume and are only slightly smaller for total volume. The gray volume estimates were small when obtained using pongid prefrontal percentage predictions, and become slightly negative using allometric predictions. Prefrontal white matter volume in humans was significantly larger than predicted (based on nonhuman species average values, one-tailed $P = 0.03$). The other measures were not significantly larger, though it is important to reiterate that our method for delineating the prefrontal is highly conservative. Thus, these values should be seen as minimum estimates for the entire prefrontal cortex.

There was a large degree of individual variation within species, including *Homo sapiens* (**Figs. 2** and **4**). For total prefrontal volumes, human individual residual values ranged from 2.9 ml to 45.2 ml (3% to 43%) larger; for gray volumes, from 11.5 ml (18%) smaller to 10.5 ml (15%) larger; and for white volumes, from 2.7 ml to 31.9 ml (9% to 79%) larger. Although six individual human values fell below the upper confidence intervals for prefrontal white volume, all individual human values nevertheless fell above the regression based upon species means (only *Cebus apella*, $n = 3$, and *Gorilla gorilla*, $n = 2$, showed this pattern among nonhuman primates). All individual human values also fell above the regressions for total prefrontal volume (also true only for *Cebus apella* and *Gorilla gorilla* among nonhuman primates), though one individual fell very close to the line.

DISCUSSION

The difference found in the proportion of prefrontal white to gray matter is not necessarily in conflict with an earlier finding that total cerebral white matter is predicted by total neocortical gray matter across primates[22]. This same study also reported that gyrification (degree of folding) in the prefrontal cortex is significantly larger in humans than predicted, even though overall gyrification of the cortex as a whole is not[22]. A tight relationship between overall gray and white volumes for the whole cerebrum does not require a uniform relationship within all subregions.

This difference between proportions of prefrontal white versus gray matter has important implications for neural development. Neural Darwinist accounts of connectional development suggest that early neuronal proliferation in some areas biases connection patterns to and from those areas, thereby substantially biasing functional processing[1]. To the extent that gray matter volume is a proxy for neuronal proliferation, such a model predicts that gray matter increases should go hand-in-hand with white matter increases in elaborated regions. Yet the present research suggests that connectional patterns themselves can vary independently of such neuronal proliferation and may not simply be the result of them. At the very least, it suggests that connectional biases (as gauged by white matter distributional patterns) may be more evident than differences

Table 2 Average percentage of cortical measure designated prefrontal

Species	N	Total volume Mean	Total volume s.e.m.	Gray volume Mean	Gray volume s.e.m.	White volume Mean	White volume s.e.m.
Homo sapiens	12	12.7	0.3	14.4	0.3	10.9	0.4
Pan paniscus	4	9.1	0.3	11.9	0.4	6.8	0.4
Pan troglodytes	6	10.9	0.8	14.1	1.1	8.3	0.7
Gorilla gorilla	2	10.7	0.5	13.7	0.8	8.3	0.2
Pongo pygmaeus	4	10.6	0.6	14.1	0.5	7.5	0.6
Pongid average	4.0	10.3	0.5	13.4	0.7	7.7	0.5
Hylobates lar	2	9.6	0.7	12.3	1.2	6.9	0.0
Cercocebus torquatus atys	4	7.9	0.6	9.8	0.7	6.2	0.8
Papio cynocephalus	2	9.2	1.4	11.2	0.5	7.5	2.0
Macaca mulatta	3	8.0	0.6	8.8	0.3	7.3	0.9
Cebus apella	3	10.0	0.1	11.4	0.5	8.6	0.2
Saimiri sciureus	4	8.3	0.6	10.6	1.0	6.3	0.3
Cercopithecoid and ceboid average	3.2	8.7	0.7	10.4	0.6	7.2	0.8

in neuronal proliferation in certain cortical areas. Recent advances in diffusion tensor MRI[30] open the possibility of detailed quantitative analysis of white matter tract patterns across species.

Determining the specific behavioral implications of the prefrontal elaboration during human evolution is of great interest. One notable unresolved question is exactly which neuroanatomical measure is the most behaviorally relevant, particularly for understanding human evolution. Should we ascribe more importance to the percentage of cerebral volume that is prefrontal, or the absolute excess prefrontal over average ape value (as shown above), or the residual (either absolute or relative) from primate expectations, or some other quantitative measure? A conclusion on this question cannot be made *a priori*, but only empirically, and may well vary for different behavioral domains. Having absolutely more cerebral volume in a region might well have important behavioral implications, regardless of allometric scaling trends[31]. To answer this question (if it is indeed answerable), it is necessary to determine, for a given behavioral domain or task, which neuroanatomical measure best predicts species differences in these behaviors.

It has long been known that species differences in behavioral abilities are generally reflected in differences in their cortical maps. Echolocating bats have greatly expanded auditory cortical regions (accounting for more than half the cortex of the ghost bat, *Macroderma gigas*, for example), whereas primarily subterranean mole species have markedly reduced visual cortical areas[32]. Within humans, variation in prefrontal cortex size has been found to be positively associated with at least one cognitive task known to be mediated by the prefrontal: the Stroop test, which tests the ability to extract and focus on relevant cues in the face of distractors[33]. Gray matter differences in the frontal lobe have been shown to be correlated with general cognitive ability, or *g*[34] (although this study did not control for possible between-family confounds[33]). Thus, it is a reasonable starting assumption that the elaboration of the prefrontal cortex did in fact have behavioral implications during human evolution, specifically involving the increased importance of the kinds of behaviors mediated by the prefrontal.

Given the general executive role of the prefrontal cortex, connections to posterior regions, to regions within the prefrontal or to both are clearly essential. As increased brain size seems to be strongly correlated with an increased number of distinct cortical areas[35], one would expect connectivity to and from the prefrontal to be particularly enhanced in humans. Such an effect would explain positive allometry of prefrontal scaling with respect to the rest of the cerebrum. That human white matter exceeds the amount predicted allometrically, however, suggests that some additional explanation is necessary. One obvious possibility is the evolution of human language, which is more complex

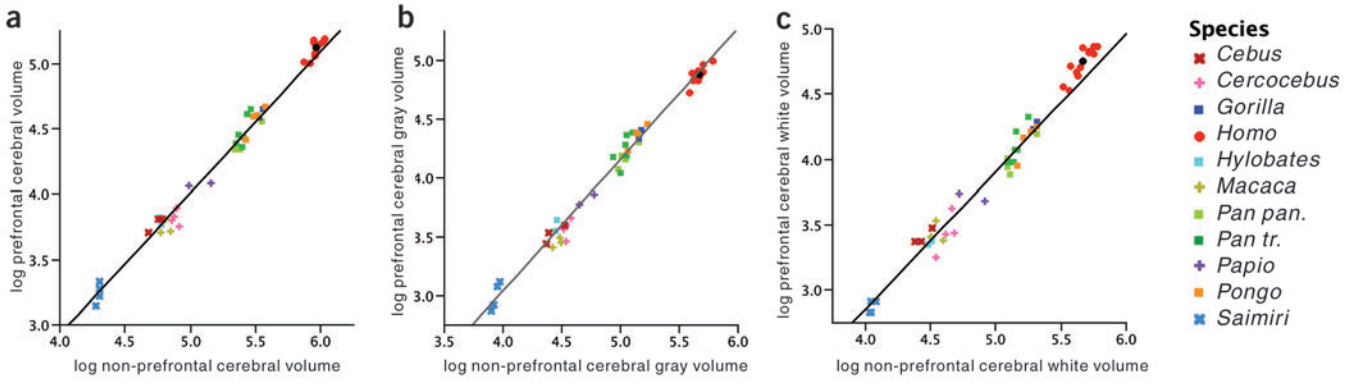


Figure 4 Relationships between prefrontal and non-prefrontal cerebral volume for all 46 specimens from 11 primate species. The mean value for *Homo sapiens* is indicated by the black dot. The lines represent least-squares regressions based on nonhuman species average values: (**a**) total (gray + white) cerebral volume; (log prefrontal cerebral volume) = –1.413 + 1.085 × (log non-prefrontal cerebral volume); (**b**) cerebral gray volume; (log prefrontal cerebral gray volume) = –1.430 + 1.118 × (log non-prefrontal cerebral gray volume); (**c**) cerebral white volume; (log prefrontal cerebral white volume) = –1.367 + 1.055 × (log non-prefrontal cerebral white volume). All relationships: $r^2 = 0.99$, $P < 0.0001$.

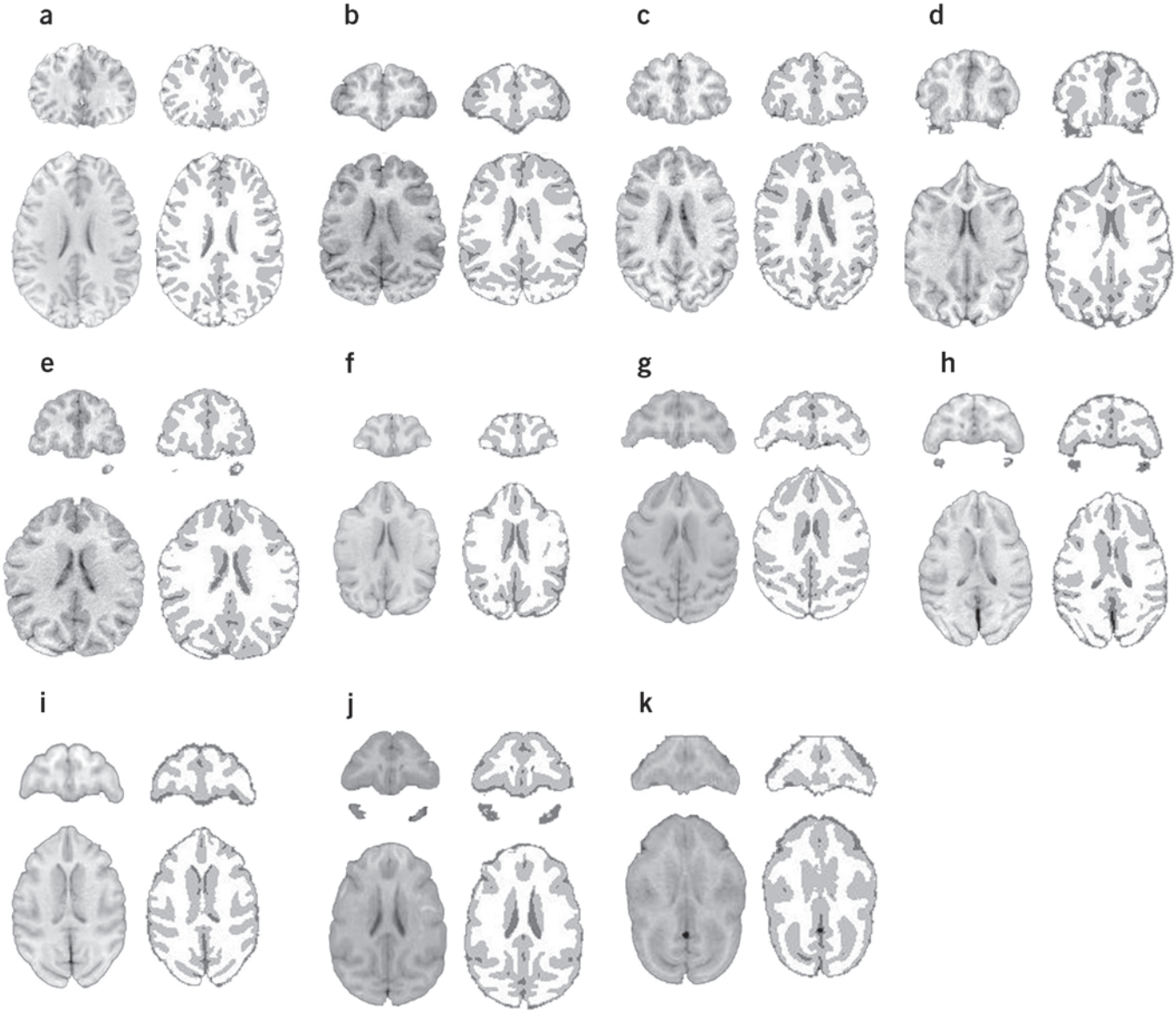


Figure 5 Segmentation examples. Two coronal (above) and two transverse (below) slices are shown for each species (scaled approximately to the same size for comparison). The leftmost coronal and transverse images show the original grayscale values; the rightmost show the corresponding segmented versions (dark gray, CSF; medium gray, gray matter; white, white matter). (**a**) *Homo sapiens*. (**b**) *Pan paniscus*. (**c**) *Pan troglodytes*. (**d**) *Gorilla gorilla*. (**e**) *Pongo pygmaeus*. (**f**) *Hylobates lar*. (**g**) *Cercocebus torquatus atys*. (**h**) *Papio cynocephalus*. (**i**) *Macaca mulatta*. (**j**) *Cebus apella*. (**k**) *Saimiri sciureus*.

and functional than any communication system seen in primates. In this regard it is important to note that an anterior portion of Broca's area is probably included in our delineation of the prefrontal (**Fig. 1**). However, a variety of anterior prefrontal regions in addition to Broca's area have been implicated in critical aspects of language processing, particularly those involving semantic information[1,9,10]. Such processing is clearly central to language. There are a number of models of natural language that specifically emphasize the importance of semantics, and it has been argued that the evolution of semantic and conceptual complexity is likely to have been the engine driving the evolution of language generally, and grammar and syntax specifically[36,37]. In addition, the importance of interconnectivity between the prefrontal cortex and numerous other brain areas has been emphasized in discussions of language evolution. Specifically, posterior cortical regions (particularly inferior parietal and temporal areas), basal ganglia, thalamus, midbrain, cerebellum and brainstem have all been implicated [1,38,39].

Other behavioral domains might also have had important roles in the increase in size of prefrontal white matter during human evolution. Brain size across primates correlates strongly with typical size of the social group, and human social group sizes are on average larger than those found in other living hominoid species[40]. This suggests social group size increased during human evolution. If so, it would have placed a premium on social information processing in general[41] (of which language is likely a special case[40]). Other behaviors mediated by the prefrontal cortex (such as planning, working memory and attention) would also have likely been useful for an increasingly complex social life.

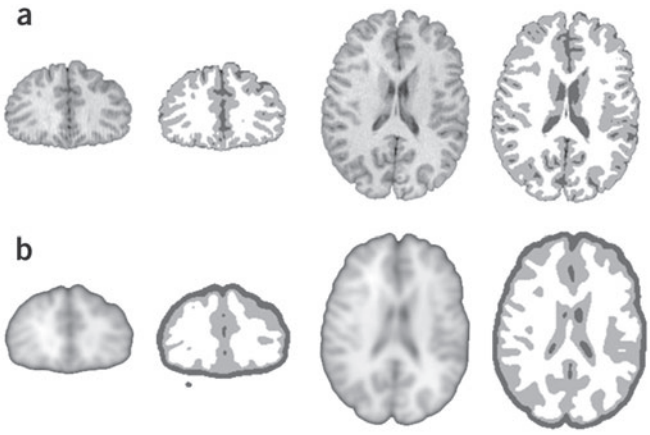


Figure 6 Effect of blurring on segmentation. Two coronal (left) and two transverse (right) slices are shown for each degree of segmentation. The leftmost coronal and transverse images show the original grayscale values; the rightmost show the corresponding segmented versions (dark gray: CSF; medium gray: gray matter; white: white matter). (**a**) Original image. (**b**) Blurred version.

An additional possible explanation involves the increasing importance of processing temporal information during human evolution. The prefrontal cortex is known to play an important role in mediating such information[8]. An understanding of causality is predicated on the ability to remember the temporal order of past events (if one cannot pay attention to the temporal order of events, one cannot reconstruct cause and effect). In addition, prefrontal regions have been shown to have a role in general ('fluid') intelligence[42], which is thought to be a measure of general problem-solving ability. Both of these abilities (keen understanding of causal relationships and general-problem solving ability, which are likely to be related at some level) would have been useful for effectively navigating an increasingly complex social existence. However, they would also have been critical for the development of elaborate technology, the extensive use of which is another behavioral domain in which humans differ from other animals. It is perhaps of interest that the earliest evidence of stone tool manufacturing (which is likely to demarcate a shift in the degree of focus on technology) occurs at ~2.5 million years ago[43]. This coincides with the beginning of hominid brain size expansion as determined from the fossil record[44]. The timing of expansion of the prefrontal cortex (let alone prefrontal white matter) is not currently known, however.

It is important to keep in mind that none of these possible explanations are mutually exclusive. Barring further information, the most prudent position to take is that all of these behavioral domains are likely to have been involved in the evolution of the prefrontal cortex. Further research into the associations between behavioral differences and prefrontal cortex size, or subdivisions of the prefrontal, both within and between species, may help further elucidate possible interpretations of the findings reported here. What is clear is that the prefrontal cortex, and specifically its connections with other cortical areas, seems to have increased disproportionately during human evolution, in contrast to the entire frontal lobe itself. This strongly suggests that the prefrontal cortex played a key role in human behavioral evolution.

METHODS

MRI dataset. The primate brain scans were obtained from Yerkes Regional Primate Research Center[22]. The scans were T1 weighted, TR = 19.0 ms, TE = 8.5 ms; slice thickness varied from 1.2 to 2 mm depending on scan; and in-plane spatial resolution varied from 0.47 to 0.70 mm^2.

Homo sapiens brain scans were obtained from healthy volunteers who had given informed written consent (approval was obtained from the institutional review boards of the University of California at San Francisco and the University of Pennsylvania). The female scans were from a previously reported sample[33]. These scans were T1-weighted, with TR = 32 ms, TE = 8 ms, with in-plane resolution of 0.94 mm^2. Female scans had slice thickness of 1.5 mm; male scans had slice thickness of 0.99 mm.

Image processing. Brain scans were processed as follows.

(i) Primate scans were corrected for fluctuations in average intensity across slices (which were evident on visual inspection) using mean-based homomorphic filtering (Analyze image processing software (AnalyzeDirect), inhomogeneity correction). Because slice differences in average intensity where not evident on the human scans, they were not filtered at this point. However, another inhomogeneity correction method was applied to all scans (human and nonhuman) during gray-white segmentation (step (iv) below). Any remaining inhomogeneity effects are unlikely to bias our results (see below).

(ii) Cerebral portions of the brain were semimanually extracted using standard flood-fill thresholding techniques (Analyze image processing software). Non-brain tissues were removed, followed by cerebellar and brain stem tissues, which were obtained as follows: in coronal view, non-cerebral tissues were removed starting at the most posterior point and proceeding anteriorly until no obvious break was evident between the midbrain and thalamus; then in transverse view, non-cerebral tissues were removed starting at the most inferior slice and proceeding superiorly until no obvious break was evident between midbrain and posterior limb of internal capsule (transition between cerebral peduncle and posterior limb of internal capsule).

(iii) Extracted cerebrums were aligned to anterior commissure–posterior commissure orientation in transverse view.

(iv) Gray and white matter regions were segmented using FAST (FMRIB's Automated Segmentation Tool, http://www.fmrib.ox.ac.uk/fsl/). This method implements a hidden Markov random field model and an associated expectation-maximization algorithm to categorize voxels into gray, white and cerebrospinal fluid (CSF) tissue types[45]. FAST also implements a correction for magnetic field inhomogeneities[46]. FAST was initialized to categorize nonzero voxels into three tissue types (corresponding to CSF, gray and white matter). Two segmented volumes were created for each specimen: white matter only and white plus gray matter. Although designed for human brain MRI, visual inspection confirmed that FAST works equally well for the nonhuman species in our sample. No gross errors of classification could be found. Example segmentations on two slices (one coronal, one transverse) for a specimen of each species are shown (**Fig. 5**). Biases potentially caused by possible species differences in image quality (because of different scanning protocols for human and nonhuman scans), voxel size or both do not seem to differentially affect prefrontal as compared with non-prefrontal volume sufficiently to account for the differences found between human and nonhuman specimens (see detailed analysis below).

(v) Stereological methods were used to estimate volume of brains in coronal orientation[28]. Stereology has long been used to accurately estimate brain volumes[47]. A three-dimensional grid of lines spaced at equal distances running in the all three dimensions is superimposed on the volume, and points where this grid falls on the object of interest (that is, white matter or gray plus white matter) are then counted. Volume (V_{est}) is proportional to the number of times the intersection points of the grid (that is, points where the grid lines in the x, y and z dimension intersect each other) fall on the object of interest. Specifically, $V_{est} = T(a/p)(P_{total})$, where T is the distance between grid intersection points in the z dimension, a/p is the area associated with each point in the x and y dimensions, and P_{total} is the sum of grid intersection points that fall on the object[28]. The specific algorithms and formulas used to calculate volume were those implemented in Analyze image processing software. We found that volume estimates were relatively insensitive to large changes in grid size, but we nevertheless used a grid size with interstices that approximated 3 mm as closely as possible (given a scan's voxel dimensions), thereby maintaining grid sizes across species. To ensure an accurate estimate, ten randomly chosen grid alignments for the x dimension were used for each subject for each measurement, and results were averaged (within subject and measurement). Measurements of white matter only and total (white plus gray) volumes were taken for both the total cerebral and prefrontal

portions. Gray matter volumes were calculated by subtraction (white plus gray minus white matter only). Prefrontal measurements were made on all coronal slices anterior to the corpus callosum (after aligning the brain to the anterior-posterior commissure line). Cerebral white and gray matter volumes defined in this way do not correspond exactly to the measures reported in ref. 22, which focused just on the cortex. The present study included all gray and white matter in the cerebrum (e.g., internal capsule, basal ganglia, thalamus).

Analysis of potential sources of bias. *Sex differences.* Male brains are bigger than female brains in humans and other primates[48,49]. Because the present dataset contains an uneven distribution of males and females across species (that is, several species are represented by more males than females, and for two (*Papio cynocephalus* and *Macaca mulatta*) there were no females), the possibility that this might bias the results was specifically addressed. Two-way ANOVAs using data from species with both male and female specimens (that is, excluding *Papio cynocephalus* and *Macaca mulatta*) showed that sex was not a statistically significant factor in predicting prefrontal percentage. This was the case for cortical white matter (effect of sex, $P = 0.41$; sex-species interaction, $P = 0.84$), gray matter (effect of sex, $P = 0.53$; sex-species interaction, $P = 0.74$) and total (gray plus white) volume (effect of sex, $P = 0.94$; sex-species interaction, $P = 0.81$). Consequently, sex was not used as a factor in statistical comparisons of prefrontal percentage measures between species. For inter-species regressions to predict human residuals, the average of male and female means was used (except for *Papio cynocephalus* and *Macaca mulatta*, for which only there were male specimens, in which case the average of male specimens only was used). However, separate regressions were also carried out using both male-only and female-only species averages. These within-sex human residual values show the same patterns and relationships seen for the overall data, indicating that the conclusions presented here are not explained by different proportions of males to females in different species.

Scan quality. Differences in scanning parameters between human and nonhuman species could conceivably affect the quantification of volume measurements if they resulted in differences in image quality between human and nonhuman scans. As mentioned above, we consider this highly unlikely based on a qualitative assessment of individual segmentations (**Fig. 5**). However, to assess the extent to which a subtle bias in scan quality might affect our conclusions, a subset of six of the human scans were purposely blurred before segmentation by FAST, and the results were compared to the values obtained with the original non-blurred versions. Blurring was accomplished by successively applying a binomial filter (Analyze) with a 3-pixel × 3-pixel mask ten times. This filter implements a nearest-neighbor average along each volume dimension, which approaches a convolution with a Gaussian as the number of iterations increases. Effectively, this spreads and smoothes the voxel values across the intensity range, thereby reducing the gray-white differentiation and successively degrading the resolution of the image. Qualitatively, this resulted in significantly poorer resolution than we observed in any of our nonhuman scans (compare **Fig. 6** to examples in **Fig. 5**). After segmentation via FAST, tissue volumes were calculated stereologically exactly as in the original non-blurred versions (**Fig. 6**). The resulting average differences in volume between blurred and original non-blurred versions for these test images are included in **Supplementary Table 1** online. Volume estimates vary between –5.8% (blurred versions yielding values 5.8% smaller than the original image) and +8.6% (blurred versions 8.6% larger). Blurring the image tends to make white volumes slightly larger, but makes gray volumes slightly smaller. The critical issue for the present study, however, concerns the extent to which the prefrontal portion is differentially affected by blurring relative to the total cerebral volume. Any biasing effects with respect to differing proportions of gray compared with white will not be critical to our conclusions unless they affect prefrontal regions substantially differently than non-prefrontal regions. For all measurements, blurring affected prefrontal and non-prefrontal portions in the same direction, though not exactly to the same extent (**Supplementary Table 1 online**). The average differences of the estimates of prefrontal percentage were quite small: +0.24 (s.e.m. = 0.19) absolute percentage points for total volume, +0.87 (s.e.m. = 0.16) for gray volume, and –0.14 (s.e.m. = 0.26) for white volume. Thus, white volume prefrontal percentage estimates tended to be slightly smaller in blurred images, whereas total volume and gray volume prefrontal percentage estimates tended to be slightly larger. This analysis suggests large amounts of blurring have relatively small effects on estimates of prefrontal percentage when compared to the average *Homo sapiens*–non-*Homo sapiens* differences that were found. *Homo sapiens* values exceed the pongid averages by 2.4% for prefrontal percentage total volume, and by 3.2% for white volume (**Table 2**). In addition, we note that total and gray volumes are larger in blurred images. Thus, if *Homo sapiens* scans were clearer than the average primate scan, our analyses suggest that this would artifactually decrease the measured *Homo sapiens*–non-*Homo sapiens* difference for these measures. For these reasons, we believe that any subtle differences in image quality that might exist in our sample (which are less obvious than the differences between blurred and non-blurred test images) are highly unlikely to materially affect the conclusion that *Homo sapiens* differs in prefrontal percentage, particularly with respect to white matter.

The possible effects of image quality differences on average human residual prefrontal values (caused by possible changes in the scaling relationships of prefrontal to non-prefrontal measurements) can be estimated by artificially adjusting nonhuman primate data to make a worst-case assessment. The analyses above suggest that any image quality biases that might exist are likely to differentially affect prefrontal areas by significantly less that 10% more than non-prefrontal areas (**Supplementary Table 1** online). Furthermore, image quality degradation seems to artificially decrease only prefrontal white volume estimates. If nonhuman scans were systematically of lower quality, then only these measures would be expected to result in inflated human residuals (through lower nonhuman primate regression lines). A worst-case assessment of such effects can therefore be accomplished by artificially inflating nonhuman prefrontal values by 10% and then recalculating human residuals. This would model a larger, more systematic image-quality bias pervading nonhuman scans than is evident on visual inspection (**Fig. 5**). Nevertheless, even in this case average human residual prefrontal white volume is still 29% larger than nonhuman primate trends predict (compared to 41% calculated on the actual data), which approaches statistical significance ($P = 0.08$, one-tailed). If nonhuman primate prefrontal total and gray volumes are similarly adjusted down by 10% (reflecting the fact that image degradation seems to artificially inflate these measures), average human residual prefrontal total volume is 31% larger than nonhuman primate trends predict (compared to 18% for actual data), and average prefrontal gray volume becomes 8% larger (compared to 3% smaller for actual data). These analyses suggest that even if pervasive, systematic biases exist as a result of differing quality of human as compared to nonhuman images, average human residual values would likely still exceed primate allometric predictions for prefrontal total and white volumes.

Inhomogeneity. Although the scans were processed to correct variations in signal intensity in different regions caused by inhomogeneities in the magnetic field, no such method of correction is perfect. If species varied with respect to the presence of subtle inhomogeneities in prefrontal but not in non-prefrontal regions, or vice versa, it is possible that this could bias the estimation of prefrontal cerebral volume compared with non-prefrontal cerebral volume. If a greater degree of inhomogeneity persists in the prefrontal cortex even after correction, then the prefrontal cortex might tend to be brighter relative to the rest of the cerebrum, and therefore more of the prefrontal cortex might be incorrectly classified as white than in the rest of the cerebrum. This could potentially bias results if it occurred differentially in human and nonhuman scans. However, if this is truly a pervasive problem in the present dataset, it should result in a positive association between the relative brightness of the prefrontal cortex (indexing the degree that inhomogeneities are biased towards the prefrontal compared with non-prefrontal areas) and the relative increase in percentage white in the prefrontal compared with non-prefrontal areas. In the present dataset, the correlation between ratio of prefrontal average intensity to non-prefrontal average intensity ((average intensity of prefrontal)/(average intensity of non-prefrontal)) and the ratio of percentage of prefrontal that is white to percentage of non-prefrontal that is white ((percentage of white in prefrontal)/(percentage of white in non-prefrontal)) is essentially zero for nonhuman primate species ($r^2 = 0.0002$, $P = 0.98$, $n = 10$). That is, species in this dataset with relatively brighter prefrontal cortices do not tend to have greater proportions of the prefrontal designated as white matter. This suggests that even if subtle inhomogeneity effects remain after the corrections applied in this study, they do not seem to affect the conclusions presented here.

Voxel size. Voxel size varied considerably across subjects, from 0.26 ml (*Saimiri sciureus*: 0.47 mm × 0.47 mm × 1.20 mm) to 1.32 ml (human females: 0.94 mm

× 0.94 mm × 1.50 mm). Conceivably, these differences might affect the ability of the algorithm to segment gray and white volumes because of partial volume effects. Two kinds of voxel resolution might be relevant here: (i) absolute size of voxels regardless of brain size and (ii) size of voxels relative to overall brain size (that is, proportion of total brain size accounted for by each voxel). Given that cortical thickness varies as a function of brain size[50], smaller brains are likely to have greater gray/white partial volume effects, holding absolute voxel size constant. Human brains in this sample have the coarsest absolute resolution but the finest relative resolution (see **Supplementary Table 2** online for average absolute and relative voxel sizes for each species in this study). The crucial question for the present study is again whether prefrontal percentage estimates are significantly affected by differences in either relative or absolute voxel size. The possible effects were assessed in two different ways. First, we artificially inflated voxel sizes in a sample of our human scans and measured the extent to which this influenced prefrontal percentage estimates. Second, we assessed the extent to which voxel size (either relative or absolute) explained any of the variation between species in prefrontal percentage measures.

The six female human scans were reformatted to contain 2 mm cubic voxels, which thereby contain six times more volume per voxel than the original versions. Because actual brain size for each of these subjects of course remains the same, this reformatting results in large increases in relative voxel size (proportion of total brain per voxel), which approximate the coarsest relative resolutions used in other species in this study (**Supplementary Table 2** online). Analysis showed that although coarser resolutions do affect the relative segmentation of gray and white, prefrontal and non-prefrontal portions are affected very similarly (and just as with the blurring study, always in the same direction for prefrontal volume compared with total cerebral volume; see **Supplementary Table 3** online). As a result, the change in prefrontal percentage amounts to only +0.12 (s.e.m. = 0.20) percentage points for total volume, –0.35 (s.e.m. = 0.11) percentage points for gray, and +0.69 (s.e.m. = 0.31) percentage points for white (**Supplementary Table 3** online). Again we note that the *Homo*/non-*Homo* differences found are substantially larger than these values (see **Table 2**). Notably, with the exception of prefrontal percentage total, these are in the opposite direction from the effects documented for artificially blurring images. Thus, the effects of these two independent potential sources of error will likely often partially offset. Also, larger relative voxel sizes (as seen in nonhuman primates) seem to artificially inflate prefrontal percentage white values, which would have the effect of decreasing the measured prefrontal percentage white differences between humans and nonhuman primates in this study, thus increasing the likelihood that the difference found for white matter volume is real. Prefrontal percentage total is largely unaffected, and prefrontal percentage gray is marginally affected (but as prefrontal percentage gray was not found to be significantly different in humans, this does not affect the conclusions presented here).

Another way to assess the possible effects of voxel size differences across species is to directly assess its association with the measures of interest. If species differences in voxel size meaningfully affect the estimation of either prefrontal percentage total, white, or gray volumes, then these measures should correlate with differences in either absolute or relative voxel size in nonhuman primate values (including *Homo sapiens* in the assessment conflates the specific species difference we are interested in with any biasing effect we are trying to estimate). For the present dataset, none of the correlations with absolute voxel size are significant in nonhuman primates (correlation between absolute voxel size and prefrontal percentage total: $r = 0.05$, $P = 0.89$; prefrontal percentage gray: $r = –0.03$, $P = 0.93$; prefrontal percentage white: $r = 0.25$, $P = 0.49$). The threefold range of variation in nonhuman primates' absolute voxel size suggests that restriction of range is not a likely explanation for these low correlations. With respect to relative voxel size, correlations with the proportion of total brain size accounted for by each voxel are significant only for prefrontal percentage total ($r = –0.76$, $P = 0.01$) and prefrontal percentage gray ($r = –0.79$, $P = 0.01$) but not for prefrontal percentage white ($r = –0.38$, $P = 0.27$). Human prefrontal percentage total falls outside the 95% confidence intervals, though the human prefrontal percentage gray does not. This is additional confirmation that our conclusions are not materially affected by possible biasing effects of relative or absolute voxel size.

Taken together, these analyses suggest that differences in human and nonhuman prefrontal percentage white and total volumes are not likely to be explained by image quality, voxel size or sex representation differences between species.

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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