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Chad J. Donahue, Washington University  
Matthew F. Glasser, Washington University  
Todd M Preuss, Emory University  
James K Rilling, Emory University  
David C. Van Essen, Washington University

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Quantitative assessment of prefrontal cortex in humans relative to nonhuman primates

Chad J. Donahue\textsuperscript{a,1}, Matthew F. Glasser\textsuperscript{a,b}, Todd M. Preuss\textsuperscript{c,d,e}, James K. Rilling\textsuperscript{d,e,f,g,h}, and David C. Van Essen\textsuperscript{a,1}

\textsuperscript{a}Department of Neuroscience, Washington University School of Medicine, St. Louis, MO 63110; \textsuperscript{b}St. Luke’s Hospital, St. Louis, MO 63101; \textsuperscript{c}Division of Neuropharmacology and Neurologic Diseases, Emory University, Atlanta, GA 30329; \textsuperscript{d}Center for Translational Social Neuroscience, Emory University, Atlanta, GA 30329; \textsuperscript{e}Yerkes National Primate Research Center, Emory University, Atlanta, GA 30329; \textsuperscript{f}Department of Anthropology, Emory University, Atlanta, GA 30329; \textsuperscript{g}Center for Behavioral Neuroscience, Emory University, Atlanta, GA 30329; and \textsuperscript{h}Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA 30329

Contributed by David C. Van Essen, March 22, 2018 (sent for review December 14, 2017; reviewed by Leah A. Krubitzer, Rogier Mars, and Jeroen B. Smaers)

Humans have the largest cerebral cortex among primates. The question of whether association cortex, particularly prefrontal cortex (PFC), is disproportionately larger in humans compared with nonhuman primates is controversial: Some studies report that human PFC is relatively larger, whereas others report a more uniform PFC scaling. We address this controversy using MRI-derived cortical surfaces of many individual humans, chimpanzees, and macaques. We present two parcellation-based PFC delineations based on cytoarchitecture and function and show that a previously used morphological surrogate (cortex anterior to the genu of the corpus callosum) substantially underestimates PFC extent, especially in humans. We find that the proportion of cortical gray matter occupied by PFC in humans is up to 1.9-fold greater than in macaques and 1.2-fold greater than in chimpanzees. The disparity is even more prominent for the proportion of subcortical white matter underlying the PFC, which is 2.4-fold greater in humans than in macaques and 1.7-fold greater than in chimpanzees.

Cerebral cortex varies dramatically in size and surface area across mammals. Human cortex is the largest among primates, with a surface area roughly threefold larger than in chimpanzees and about 10-fold larger than in the intensively studied macaque monkey (1–6). Many studies have reported that association cortex (prefrontal, temporal, and parietal regions implicated in higher cognition and affect (7–9)) is disproportionately larger in humans relative to nonhuman primates (10–16). However, other studies report different conclusions, especially for prefrontal cortex (PFC) (17–19), resulting in an ongoing controversy (20).

Analyses of this type are often viewed through the lens of allometry by comparing the size of a given brain region with another measure, such as overall brain size, across a range of species. Allometric scaling implies a linear relationship when plotting data on a logarithmically scaled plot, where the slope of the best-fitting line may show positive (slope > 1; hypermetric), isometric (slope = 1), or negative (slope < 1; hypometric) allometry. Furthermore, a significant positive deviation of a single species from an allometric relationship would be referred to as “exceptional” [e.g., human brain weight relative to body weight is exceptionally large compared with other mammals (21)]. Some studies have reported a positive allometric relationship across primate species based on the size of the PFC and the rest of the brain using structural volumes (18, 22). Others have compared PFC to lower-order cortical areas and reported a deviation in humans from the allometric trend when comparing the size of the PFC with that of primary visual (area V1) and frontal motor cortex (12, 23). In contrast, Gabi et al. (17) recently reported evidence for an isometric relationship using neuronal counts for PFC vs. other cortical regions.

Other morphometric analyses inform but do not resolve this debate. Semendeferi et al. (19, 24) reported that although frontal, temporal, and parietal lobes are larger in humans than in apes, the fraction of total cortex belonging to each region is similar across species. By contrast, studies using surface-based interspecies registration (mapping) constrained by putative cortical homologs suggest that surface area in these regions is disproportionately larger (20-fold or more in places) in humans compared with macaques, whereas early sensory regions (e.g., area V1) are expanded as little as twofold (3–5); there are also regional differences in estimated PFC extent when comparing marmoset, capuchin, and macaque monkeys (25). Furthermore, cortical myelin maps derived from in vivo MRI reveal a greater extent of lightly myelinated cortex in both association and higher-order sensory regions in humans compared with chimpanzees and macaques, whereas species differences appear more modest in heavily myelinated early sensorimotor regions (6).

These conflicting results and interpretations regarding PFC scaling may largely reflect methodological differences among studies (20, 23). One such difference is the region with which the PFC is being compared. Bush and Allman (22) compared frontal

\textbf{Significance}

A longstanding controversy in neuroscience pertains to differences in human prefrontal cortex (PFC) compared with other primate species; specifically, is human PFC disproportionately large? Distinctively human behavioral capacities related to higher cognition and affect presumably arose from evolutionary modifications since humans and great apes diverged from a common ancestor about 6–8 Mya. Accurate determination of regional differences in the amount of cortical gray and subcortical white matter content in humans, great apes, and Old World monkeys can further our understanding of the link between structure and function of the human brain. Using tissue volume analyses, we show a disproportionately large amount of gray and white matter corresponding to PFC in humans compared with nonhuman primates.

Author contributions: C.J.D., M.F.G., and D.C.V.E. designed research; C.J.D. performed research; C.J.D., M.F.G., T.M.P., J.K.R., and D.C.V.E. analyzed data; and C.J.D., M.F.G., T.M.P., J.K.R., and D.C.V.E. wrote the paper.

Reviewers: L.A.K., University of California, Davis; R.M., Radboud University Nijmegen; and J.B.S., Stony Brook University.

The authors declare no conflict of interest.

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Data deposition: All data related to this study are freely available via the BALSA database (https://balsa.wustl.edu/study/019).

To whom correspondence may be addressed. Email: donahue@wustl.edu or vanessen@wustl.edu.

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gray matter with remaining neocortical gray matter, whereas Smaers et al. (23) compared the PFC with more evolutionarily conserved, lower-order cortical regions such as primary visual cortex (area V1). Some studies focus on volumetric differences in cortical gray matter and/or the extent of the underlying white matter (26), whereas others consider counts of neurons for gray matter and nonneuronal cells for white matter (17). Most striking are differences in delineating what constitutes the PFC. A lack of comparative architectonic or other data that could directly identify the location of homologous areas and regions has led some investigators to instead invoke neuroanatomical proxies for the PFC. For example, Semendeferi et al. (19) analyzed the entire frontal lobe, whereas Smaers et al. (27) investigated cumulative frontal lobe volumes starting respectively from its anterior (prefrontal) and posterior (motor) extremes. Schoenemann et al. (26) and Gabi et al. (17) explicitly approximated the PFC using a morphological surrogate: cortex anterior to the genu of the corpus callosum. However, the accuracy of this genu-based approximation has yet to be critically assessed.

Generally, “PFC” has referred to frontal lobe association cortex lying anterior to motor and premotor regions. Many studies have used cytoarchitectonics in efforts to objectively delineate the PFC. Cortical layer 4 can appear granular (with a high density of small neurons), agranular (lacking a well-defined layer 4), or dysgranular (having a subtle layer 4 with a modest density of small neurons). The earliest delineation of the PFC was Brodmann’s (15) regio frontalis, consisting of granular frontal and orbital cortex. More recent studies consider the PFC to include both granular and dysgranular regions of medial frontal and orbitofrontal cortex in human (28) and macaque (29) and lateral frontal cortex in both species (30–32). Geyer (33) analyzed human premotor and prefrontal regions and reported that agranular cortex in posterior Brodmann area 6 (premotor) transitions anteriorly to dysgranular cortex by a graded cytoarchitectonic transition rather than by a sharp boundary. Consistent with this hypothesis, functional neuroimaging analyses implicate some agranular as well as dysgranular frontal lobe areas in higher cognitive function (34).

To address differences in PFC across several primate species, we used structural MRI datasets from humans, chimpanzees, and macaque monkeys to generate cortical surface models of individual subjects, estimate cortical myelin content and thickness, and register individuals onto species-average atlases. We then utilized available data to delineate the PFC in several ways. We present PFC delineations based on architectonic criteria and on the callosal genu PFC approximation in all three species and on combined functional and architectonic criteria for humans and macaques. Because we analyzed only three species, we could not create a robust nonhuman primate allometric scaling regression to evaluate whether data points for humans are exceptional. Instead, we focus on the relative scaling of the PFC across species compared with non-PFC cortex, area V1, and area 4.

**Results**

**Cytoarchitectonic Designations Allow Surface-Based PFC Delineation Across Species.** Based on cytoarchitectonics, we delineated a conservative PFC boundary (Fig. 1, regions filled in red) that includes granular and dysgranular frontal lobe cortex anterior to motor and premotor cortex, as has been proposed for both humans (28, 31) and macaques (35). However, agranular regions of medial frontal and orbitofrontal cortex have been implicated in higher cognitive function, and we consider it appropriate to include these areas of frontal lobe cortex that are functionally neither motor nor premotor in a liberal PFC delineation (Fig. 1, additional regions filled in blue).

For human cortex, we used individual-subject parcellations from 60 unrelated subjects taken from the 210V group [the validation group of the Human Connectome Project (HCP) Multimodal Parcellation (HCP_MMP1.0), which used an areal classifier that matched individual-subject feature vectors to an initial group-average multimodal parcellation (34)]. For the macaque, a pan-hemispheric composite of published parcellations (36–38) was mapped onto a species-average macaque atlas (39) (Yerkes19) and then to the constituent 19 individuals for morphometric analyses. This composite includes several modified areas, marked as “prime,” that reflect a combination of previously described areas. For example, area 10 found in dorsolateral PFC is an amalgamation of area 10 as reported by Ferry et al. (36) and Paxinos et al. (38). Some of these areas then
underwent further subdivision: areas 24a, 24b, and 24c were subdivided into anterior and posterior segments (e.g., 24aa and 24ap, respectively) based on descriptions of area 24 as dysgranular anteriorly with associated cognitive-related function transitioning to an agranular cytoarchitecture posteriorly associated with motor function (30, 40, 41). The Bailey et al. chimpanzee architectonic parcellation (42) includes areal designations on a series of histological section contours. We mapped areal designations from section contours to corresponding MRI sections in an individual chimpanzee brain and from there to our surface-based chimpanzee atlas (Supporting Information). We then drew estimated areal boundaries on the atlas surface, aided in dorsolateral cortex by myelin maps, cortical thickness maps, and their gradients.

For each species, an area was considered part of conservative PFC based on cytoarchitecture and inclusion in published PFC delineations. Areas specific to the human liberal PFC delineation include inferior frontal junction areas (IFJa/p), i/s6-8, and 55b of the lateral frontal cortex, a/p24, 25, a32pr, d/p/s32, and the superior frontal language area (SFL) of the medial frontal cortex, and posterior orbital frontal cortex (pOFC). For the macaque, exclusively liberal PFC areas include medial frontal areas 24aa, 24ba, 24ca, 25, and 32 and orbitofrontal areas 13a and 14c. The frontal eye fields are sometimes considered part of the PFC (40, 43) but were excluded here because of their stronger association with premotor regions than with cognitive regions in terms of moderate rather than sparse myelin content and their functional connectivity (34). Frontal eye fields correspond to the frontal eye field (FEF) and premotor eye field (PEF) areas in humans; area 45b in the macaque is moderately myelinated and overlaps with anatomically and functionally defined FEF (44).

Given the paucity of functional data for the chimpanzee, we focused only on a conservative PFC delineation based on the presence of granular/dysgranular cytoarchitecture and on myelin patterns. We identified Bailey et al. agranular areas as motor (FA), premotor (FB and FBA), and cingulate (LA and FL). More anterior regions were designated as PFC, except for FDF, which is moderately myelinated and likely corresponds to FEF. Medially, our chimpanzee PFC delineation includes areas FDL, FH, and FG but excludes LA and FL. (See Supporting Information for additional details and discussion of putative homologs. Figure S1 illustrates the chimpanzee parcellation. Tables S2 and S3 provide information and references for areal cytoarchitecture and cognitive-related designations for human and macaque PFC areas.)

Structural Cortical Features Aid in Delineating the PFC. Maps of estimated myelin content based on the T1-weighted/T2-weighted (T1w/T2w) intensity ratio (6, 45) provide a useful architectural marker for identifying cortical regions and areas across species. Spatial gradients of these myelin maps can provide objective evidence of sharply defined architectonic transitions (e.g., from dense to moderate or light myelination; see ref. 45). Fig. 2 illustrates myelin maps and their spatial gradients for each species in relation to our three PFC delineations. These reveal important patterns and correlations across measures, but the relationship to PFC boundaries is complex and differs for dorsolateral, ventrolateral, and medial regions.

In dorsolateral cortex, the heavily myelinated primary motor cortex (area 4; Fig. 2, Top Row, outlined in black) and the moderately myelinated premotor strip (directly anterior to area...
mainly green in human; green and yellow in chimpanzee, mainly orange-yellow in macaque) provide useful landmarks across species. In the macaque, the thickness map and its gradient were also useful, particularly for posterior area 4 (Supporting Information). In all three species, a myelin gradient ridge (Fig. 2, Second Row) runs along part of the anterior border of area 4. Anterior to this premotor/primary motor gradient ridge is another gradient ridge. In the human, this anterior gradient ridge aligns well with the liberal PFC border. In the macaque, both conservative and liberal PFC borders run in the general vicinity of the anterior myelin gradient ridges, but the correlation is not good for either. The border of chimpanzee conservative PFC follows the ridge closely in this region.

In ventrolateral and ventral regions, lightly myelinated PFC in all three species is adjoined by even more lightly myelinated cortex in the anterior insula (Fig. 2, Top Row, indigo and black) and orbitofrontal cortex (Fig. 2, Third Row). However, the most prominent myelin gradient does not coincide with published architectonic PFC delineations [also, in the macaque and chimpanzee datasets, orbitofrontal cortex was not as accurately segmented owing to localized signal dropout and distortion of T1w relative to T2w images]. In medial cortex, the PFC is lightly myelinated dorsally and very lightly myelinated ventrally in all three species, but none of them shows a clear myelin gradient running along the PFC boundary. Thus, there are strong cross-species similarities in myelin maps in and near the PFC, but only in the dorsolateral PFC of human and chimpanzee do we consider myelin gradients strongly informative about PFC borders. Cortical thickness maps and their gradients were of limited utility for delineating PFC borders (Fig. S4).

### Genu-Based Morphological Surrogate Underestimates PFC Extent.

Fig. 3 illustrates the range of individual variation in the location of liberal, conservative, and genu-based PFC borders as defined for each species. Probability maps indicate most (yellow) and least (black) common locations of each border. Important species differences are revealed by comparing parcellation-based PFC delineations (both liberal and conservative) with genu-based PFC approximations (Fig. 3, Bottom Row). In dorsolateral frontal cortex, the macaque and chimpanzee genu-based PFC border runs somewhat anterior to the moderately myelinated region adjacent to premotor cortex, mostly anterior to the conservative delineation. By visual inspection, the genu-based delineation in the human more substantially underestimates PFC spatial extent compared with both liberal and conservative delineations. This observation is evaluated quantitatively in the next section.

### Human PFC Is Absolutely and Relatively Large Compared with Nonhuman Primates.

Table 1 reports the mean volume for total cortical gray matter, primary visual area V1, and primary motor area 4 and mean volumes relating to PFC delineations, along with SDs. These volumes were calculated for both hemispheres of each individual subject and then were averaged. Also provided

Table 1. Cortical gray matter volumes across species

<table>
<thead>
<tr>
<th>Species</th>
<th>Total volume</th>
<th>Genu-based PFC (%)</th>
<th>Conservative PFC (%)</th>
<th>Liberal PFC (%)</th>
<th>Area V1 (%)</th>
<th>Area 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human (n = 60)</td>
<td>512 ± 55</td>
<td>77.2 ± 11 (15)</td>
<td>105 ± 13 (21)</td>
<td>131 ± 16 (26)</td>
<td>14.0 ± 2.0 (2.72)</td>
<td>11.2 ± 1.6 (2.18)</td>
</tr>
<tr>
<td>Chimpanzee (n = 29)</td>
<td>134 ± 13</td>
<td>18.5 ± 2.6 (14)</td>
<td>23.2 ± 2.4 (17)</td>
<td>7.5 ± 0.8 (5.63)</td>
<td>8.1 ± 1.2 (6.04)</td>
<td></td>
</tr>
<tr>
<td>Macaque (n = 19)</td>
<td>34.4 ± 2.9</td>
<td>3.34 ± 0.5 (10)</td>
<td>4.4 ± 0.5 (13)</td>
<td>3.3 ± 0.4 (10.7)</td>
<td>1.4 ± 0.2 (4.46)</td>
<td></td>
</tr>
</tbody>
</table>

Mean volumes of human, chimpanzee, and macaque cortical gray matter for entire cortex; genu-based, conservative, and liberal delineations of prefrontal cortex; primary visual area V1, and primary motor area 4, as well as SDs. Percentages in parentheses are percentages of total cortical gray matter volume. See Dataset S1 for additional measures.
(in parentheses) is the percentage of each PFC region of interest (ROI) and cortical area volume relative to total volume of the neocortex (see Supporting Information for individual variance in percentage values and Dataset S1 for additional measures).

After averaging the left and right hemispheres, computed mean gray matter volumes were 512 ± 55 cm³, 134 ± 13 cm³, and 34.4 ± 2.9 cm³ for human, chimpanzee, and macaque, respectively, indicating that the volume of human cortical gray matter is 15-fold greater than that in the macaque and roughly fourfold greater than that in the chimpanzee. Mean surface areas were 1,843 ± 196 cm² for humans, 599 ± 53 cm² for chimpanzees, and 193 ± 13 cm² for macaques; mean cortical thicknesses were 2.7 ± 0.1 mm, 2.6 ± 0.1 mm, and 2.0 ± 0.1 mm, respectively (SDs are of means across subjects).

As shown by our two parcellation-based delineations, the proportion of PFC gray matter volume is up to 1.9-fold greater in humans compared with macaques (26% vs. 14% for the liberal delineation; 21% vs. 13% for the conservative delineation) and 1.2-fold greater compared with chimpanzees (21% vs. 17% for the conservative delineation). The genu-based PFC approximation shows a more moderate species difference, constituting 15% of human cortical gray matter volume compared with 14% in the chimpanzee and 10% in the macaque. Cortical volume computed using the genu-based proxy for PFC underestimates the parcellation-based delineations in all three species but most prominently in humans.

Scaling Relative to Primary Visual and Motor Areas. To quantify how the PFC has scaled relative to more evolutionarily conserved cortical areas, we analyzed primary visual cortex (area V1) and primary motor cortex (area 4) in terms of their cortical gray matter volume, surface area, and cortical thickness in humans, chimpanzees, and macaques (see Fig. 2 for delineations, Dataset S1 for detailed measures, and Supporting Information for additional methodological details).

In humans, chimpanzees, and macaques, respectively, the mean V1 volume was 14.0 ± 2 cm³, 7.5 ± 0.8 cm³, and 3.3 ± 0.4 cm³; the surface area was 69.7 ± 9.4 cm², 47.2 ± 4.7 cm², and 21.6 ± 1.8 cm²; and the cortical thickness was 2.0 ± 0.1 mm, 2.0 ± 0.2 mm, and 1.8 ± 0.1 mm. The PFC volume is similar to that of V1 in the macaque but is severalfold larger than V1 in humans. Surface area followed a similar trend: PFC surface area is considerably greater than that for the macaque (0.63), indicating a 35–40% relative increase in the total white matter-to-gray matter ratio in humans and chimpanzees relative to the macaque. Genu-based PFC white matter-to-gray matter ratios are 0.68 in human, 0.46 in chimpanzee, and 0.33 in macaque. Analyzed differently, PFC white matter is a larger fraction of total white matter in humans (12%) than in chimpanzees (7%) or macaques (5%). This 2.4-fold relative difference in PFC white

**Table 2. Subcortical white matter volumes across species**

<table>
<thead>
<tr>
<th>Species</th>
<th>Total volume</th>
<th>Genu-based PFC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human (n = 60)</td>
<td>443 ± 62</td>
<td>52.3 ± 10.2 (12)</td>
</tr>
<tr>
<td>Chimpanzee (n = 29)</td>
<td>119 ± 12</td>
<td>8.5 ± 1.9 (7)</td>
</tr>
<tr>
<td>Macaque (n = 19)</td>
<td>21.8 ± 2.5</td>
<td>1.1 ± 0.2 (5)</td>
</tr>
</tbody>
</table>

Volumes of human, chimpanzee, and macaque subcortical white matter for entire cortex and genu-based delineations of PFC. PFC percentages in parentheses are relative to total volume. See Dataset S1 for additional measures.

**White Matter Volumes.** Table 2 reports the total volume of subcortical white matter for each species along with volumes of white matter anterior to the genu-based PFC proxy, which is the only parcellation having a well-defined posterior extent of PFC white matter and hence amenable to analysis of white matter volumes. Total white matter volumes for humans, chimpanzees, and macaques were on average 443 ± 62 cm³, 119 ± 12 cm³, and 21.8 ± 2.5 cm³, respectively (see Dataset S1 for additional measures).

The ratio of total white matter to gray matter volume is similar in the human and chimpanzee (0.87 and 0.89, respectively), considerably greater than that for the macaque (0.63), indicating a 35–40% relative increase in the total white matter-to-gray matter ratio in humans and chimpanzees relative to the macaque. Genu-based PFC white matter-to-gray matter ratios are 0.68 in human, 0.46 in chimpanzee, and 0.33 in macaque. Analyzed differently, PFC white matter is a larger fraction of total white matter in humans (12%) than in chimpanzees (7%) or macaques (5%). This 2.4-fold relative difference in PFC white

**Fig. 4.** Log-scale plots comparing PFC gray and white matter volume with reference values across species (macaques, diamonds; chimpanzees, squares; humans, circles). (A) Volumes of conservative PFC (red), non-PFC (black), and area V1 (green) gray matter plotted against total cortical gray matter volume. Volumes of area 4 are plotted with solid magenta markers without a corresponding linear fit. (B) PFC gray matter volume plotted against the volume of the primary visual cortex. Blue, red, and black markers indicate liberal, conservative, and genu-based PFC delineations, respectively. (C) Genu-based PFC white matter volume plotted against total white matter volume. For all panels, solid lines represent the best fit using mean macaque, chimpanzee, and human data points; dotted lines represent 95% CIs.
matter between humans and macaques (12% vs. 5%) markedly exceeds the 1.5-fold difference in the genu-based gray matter volumes.

**PFC Exhibits Positive Allometric Scaling for Humans and Nonhuman Primates.** Fig. 4 illustrates several logarithmically scaled comparisons that represent the size of the PFC across species relative to reference measures. To assess the differential scaling of different cortical regions, we plotted the volumes of PFC gray matter, non-PFC gray matter, area V1, and area 4 against the volume of total cortical gray matter (Fig. 4A). We additionally compared PFC gray matter with the more evolutionarily conserved area V1 (Fig. 4B) and compared PFC white matter with total white matter (Fig. 4C).

When using total cortical gray matter as a reference (Fig. 4A), the scaling of conservative PFC gray matter as defined by the regression line through the mean macaque, chimpanzee, and human data points exhibits positive allometry (slope of 1.18; 95% CI 1.16–1.18). Additionally, this regression of PFC across total cortex appears steeper than that of other comparators: non-PFC cortex (slope of 0.97; 95% CI 0.96–0.97) and visual area V1 (slope of 0.53; 95% CI 0.49–0.54). Analysis of covariance (ANCOVA) across the three regression slopes indicated they are significantly different from one another (Supporting Information). Interestingly, data for area 4 across the three species deviate markedly from an allometric fit (linear on a log-log plot). Area 4 volume is similar to that of V1 in humans and chimpanzees but is much smaller than that in the macaque (Discussion). When, instead, the evolutionarily conserved visual area V1 is used as a reference (Fig. 4B), the PFC scales with even greater positive allometry (slope of 2.21; 95% CI 2.05–2.24). Finally, PFC white matter scaled with total white matter volume with positive allometry (slope of 1.27; 95% CI 1.26–1.31).

**Discussion.** Using a cortical surface-based approach, we have presented a comparative delineation and analysis of frontal association cortex in humans, chimpanzees, and macaques. In addressing a longstanding controversy, we report strong evidence for a greater proportion of human PFC gray matter volume compared with two nonhuman primates and an even greater species difference for PFC white matter volume.

**Prefrontal Cortex Can Be Delineated Using Cytoarchitectonic and Functional Criteria.** Our criteria for areal inclusion in the PFC entailed judgment calls based on the preponderance of available evidence. Our conservative criteria relating to granular/dysgranular cytoarchitecture, although guided by evidence in the literature, is not a simple consensus view. Our liberal delineations in the human and macaque (areas reported to have agranular cytoarchitecture) entailed subjective assessments regarding what cognitive task contrast activation or other functional information relative to neighbors warrants inclusion. A notable exception to these criteria across species is the exclusion of frontal eye fields: area FEF in humans, 45b in macaques, and FDF in chimpanzees. While these areas are cytoarchitecturally granular/dysgranular and receive thalamic inputs primarily from the mediodorsal (MD) nucleus, their functional relationship to eye movement led to their placing them in the premotor category as opposed to cognitive-related PFC [see Supporting Information and Supplementary neuroanatomical results in Glasser et al. (34)]. Additionally, some areas in the macaque composite parcellation (e.g., anterior and posterior subdivisions of areas 24a, 24b, and 24c) might reasonably be reassigned to account for a gradient in cytoarchitecture, primarily in areas that extend posteriorly into densely myelinated cortex. However, plausible alternative choices for PFC extent in any of the species would not negate our main conclusion that the relative size of the PFC in the human lineage is larger than that in nonhuman primates. For example, inclusion of frontal eye field areas FEF and 45b in humans and macaques (0.52% of cortical gray matter volume in humans and 0.47% in the macaque; Dataset S1) would not materially affect our conclusions. For chimpanzees, the lack of functional imaging data limited our analysis to conservative and genu-based PFC delineations, which were guided by the Bailey et al. (42) cytoarchitectural atlas in terms of cytoarchitecture and plausibility of putative cortical homologs. These putative homologies were based on descriptions of cytoarchitecture and are by no means conclusive; however, they allowed a first-order comparison with humans and macaques. Explicit regional boundaries, however, were drawn based on visual inspection and comparison of maps of cortical myelin content, cortical thickness, and their associated spatial gradients (indicative of areal transitions) across species. Nevertheless, our candidate chimpanzee PFC boundary between premotor and prefrontal cortex warrants further analysis using modern architectonic and/or imaging methods.

Besides the architectonic, functional, and morphological criteria invoked in our study, other types of information have been proposed for delineating the PFC in various mammalian species. These include the distribution of dopaminergic projections and a prominent level of projections from the MD nucleus of the thalamus (46–48). Neither of these metrics, however, has been shown to be adequately specific to provide strong diagnostic criteria for delineating the PFC (32, 40); Dopaminergic projections are prominent throughout the primate brain and are not demonstrably overrepresented in granular frontal cortex (49, 50) compared with more posterior neocortex. Similarly, MD thalamic projections, while particularly prevalent in granular frontal cortex and thus a meaningful guide, are also present across the precentral motor region as well as more posterior regions (51).

**Human PFC Volume Is Disproportionately Large.** We used a surface-based approach (1, 2, 4) derived from structural MRI to generate our analysis of cortical volumes. Our sample size includes 60 humans, 29 chimpanzees, and 19 macaques, thereby enabling estimates of variability in each population. We found the proportion of PFC cortical gray matter volume in humans to be up to 1.9-fold greater than in macaques and up to 2.2-fold greater than in chimpanzees. The differences in the proportion of PFC subcortical white matter volume are even more pronounced, with humans exhibiting a 2.4-fold greater proportion than in macaques and a 1.7-fold greater proportion than in chimpanzees. Thus, consistent with several previous studies (2, 5, 6, 12, 23, 26, 27), our results strongly support the hypothesis that the proportion of cortical gray and white matter volumes attributed to frontal association cortex is larger in humans than in nonhuman primates. Furthermore, the absolute size of the conservatively delineated human PFC is 4.5-fold larger than in the chimpanzee, which is especially striking considering the more modest difference in the size of the primary visual cortex (1.9-fold larger in humans). Coupled with the evidence that humans have substantially more PFC white matter volume (23, 27), this points to an impressively greater amount of neural machinery associated with the PFC in humans compared with nonhuman primates.

Scaling relative to total cortical volume, however, is impacted by the similarity in scaling between the PFC and other cortical association areas. Therefore, scaling of PFC volume based on that of primary sensory and motor areas can shed light on allometric differentiation of different cortical regions (12, 23). Our results indicate a hypometric scaling of V1 with respect to cortical volume relative to the hypermetric scaling of PFC (Fig. 4A) and a prominently hypometric scaling of PFC with respect to V1 (Fig. 4B). The hypometric scaling of V1 is likely related to the high visual acuity and importance of vision in all three species, resulting in only modest species differences in the size of V1. For area 4, the lack of an allometric scaling relationship prevented an
and Table 2), corroborating earlier reports (23; 27). It is intriguing to speculate on the neuroanatomical basis of these striking species differences. Given the aforementioned evidence (17) that PFC neuronal density is relatively low in humans vs. nonhuman primates, the density of output axons from human PFC projection neurons (i.e., pyramidal cells) is presumably lower as well. A disproportionately large white matter volume underlying human PFC might instead reflect (i) an increased density of afferent projections from distant (non-PFC) regions contributing to an increased axonal density within human PFC gray matter; (ii) a disproportionately high percentage of human PFC output axons that traverse the underlying white matter but nonetheless terminate within other PFC targets; (iii) a disproportionately large average axonal diameter in human PFC white matter; and/or (iv) a disproportionately high degree of axonal branching within human PFC white matter. Disentangling these and other possibilities is unlikely to be easy but might become feasible with further advances in neuroanatomical methods.

**Methods**

**Data Collection.** We used publicly available healthy young adult human structural T1w and T2w scans acquired at 0.7-mm isotropic resolution as part of the HCP, using the HCP’s standard protocol (60). Although we were able to balance by sex in choice of human subjects, this was not feasible for nonhuman primates due to data availability. From a larger HCP subject set, 60 unrelated subjects (30 male and 30 female) were selected for analysis from the S500 HCP data release. Human data were acquired, processed, and publicly released by the Human Connectome Project (HCP). The HCP obtained informed consent from all participants and was approved to conduct human studies by the Washington University in St. Louis Institutional Review Board (#201105040 date: June 2, 2011). For the macaque and chimpanzee structural T1w and T2w scans used previously acquired at the Yerkes National Primate Research Center at Emory University. A group of 19 adult macaques (1 male and 18 female) was scanned at 0.5-mm isotropic resolution. A group of 29 adult chimpanzees (all female) was scanned at 0.8-mm isotropic resolution. For the macaque and chimpanzee datasets, localized signal dropout was observed in anterior insular and orbitofrontal cortex. Nonhuman primate data were acquired through separate studies covered by animal research protocols approved by the relevant institutional committees.
For each human subject, T1w and T2w scans were initialized using the minimal preprocessing pipelines developed for the HCP (60) to maximize alignment across imaging modalities and minimize distortions and blurring of the data. Field maps were available, and readout distortion was corrected in humans. Intersubject registration to a group-average atlas surface was performed using a two-stage process based on the MSM algorithm (58), where an initial gentle stage is driven by cortical folding patterns and a more aggressive second stage utilizes cortical areal features of myelin, resting-state network maps, and visuotopic maps (34).

A version of the HCP pipelines adapted for nonhuman primates (HCP-NHP pipelines) (39) was used to process macaque and chimpanzee T1w and T2w structural scans. Initially, the FreeSurfer pipeline aligns T1w and T2w volumes to native anterior commissure–posterior commissure (AC–PC) space and performs brain extraction, cross-modal registration, bias field correction, and nonlinear volume registration to atlas space using the FMRIB Software Library (FSL; University of Oxford) (61). A nonhuman primate-specific pipeline, FreeSurferNHP, differs from the HCP FreeSurfer pipeline in the following ways: (i) using nonhuman primate volume templates and adjusting the brain size parameter to 80 mm for the macaque and 120 mm for the chimpanzee and (ii) converting the data into a “fake” 1-mm × 1-mm × 1-mm space to conform to FreeSurfer requirements without interpolation (62). This last modification allows the full resolution of the nonhuman primate data to be used for surface generation. Species-specific volume and surface templates were used for registration before transformation back into the 0.5-mm input space. Cortical thickness is then computed, modifying the maximum cortical thickness parameter (from a default value of 5 mm) in the FreeSurfer _mri_make_surfaces_ command to conform to scan resolution as 5/revolution mm to ensure that the fake 1-mm space does not set too low a cap on the cortical thickness (0.5 mm data faked to 1 mm would make a 5-mm cortical thickness limit into a 2.5-mm cortical thickness limit if not adjusted).

The PostFreeSurfer pipeline uses MS-M-Sulc surface registration, a version of MS-M where alignment is driven by cortical shape (FreeSurfer’s “sulc” (sulcal) measure). The pipeline produces a high-resolution 164-k surface mesh (~164,000 vertices per hemisphere), as well as two lower-resolution meshes (32 k/10 k for macaque and 32 k/20 k for chimpanzee). In addition to surface reconstruction, myelin maps (average maps of myelin content across the cortical layers) are created based on the T1w/T2w ratio (6, 45, 63). However, the cortical thickness and myelin maps are likely biased in regions (the cortical layers) are created based on the T1w/T2w ratio (6, 45, 63).

**Calculation of Cortical Gray Matter and White Matter Volumes.** Total cortical volumes were determined by isolating the cortical gray matter ribbon (as defined by the space between white and pial surfaces) and the underlying white matter (as defined by FreeSurfer segmentation) in the native subject space. Total cortical surface areas and mean cortical thicknesses were computed for each subject using the native midthickness surface mesh and excluding the medial wall, using a revised medial wall demarcation for the macaque (i.e., excluding hippocampal cortex and other minor adjustments) rather than a published version (39). For each conservative and liberal parcellation-based PFC delineation, constituent areas were adjourned to create contiguous PFC surface-based ROIs. In humans, these ROIs were created on each subject’s 32-k mesh using each subject’s individual HCP-MMP1.0 parcellation and then were mapped to each subject’s native space using an existing mapping between the two mesh resolutions. In macaques, these ROIs were created on a 164-k mesh using the composite parcellation defined on the Yerkes19 group-average surface and subsequently were registered to each subject’s native surface mesh. Similarly, the chimpanzee ROIs were created.
on the Yerkes29 164-k surface mesh and were mapped to native subject meshes. Genu-based ROIs were created by including all surface vertices rostral to a coronal slice of the AC-PC aligned volume at the genu of the corpus callosum. The approximation of PCC used in previous studies (17, 26). Volume measurements were determined by summing the volumes of individual polygonal wedges within each ROI, where each wedge is defined by a triangle in the white surface and the corresponding triangle in the pial surface. This process was performed on each individual subject (human, n = 60; macaque, n = 19; chimpanzee, n = 29), and the mean and SD of all subjects were reported for each case (Table 1). This process is illustrated for an exemplar human in Fig. 5.

Data Availability. All data related to this study are freely available via the BALSa database (https://balsa.wustl.edu/) at https://balsa.wustl.edu/study/show/2u7V.