# Is prefrontal white matter enlargement a human evolutionary specialization?

**To the Editor:**

Using a comparative volumetric analysis of MRI scans of brains from 11 primate species (including monkeys, apes and humans), Schoenemann and colleagues[1] claim that the prefrontal white matter of humans is enlarged compared to that of other primates. This would suggest that the evolution of human cognitive capacities mediated by prefrontal circuitry relies on enhanced interconnectivity. Problems with the authors' definition of the prefrontal sector and assessment of human deviations from scaling trends, however, suggest that these conclusions are not well supported.

Unlike the frontal cortex, which can be reliably demarcated by the central sulcus[2], the borders of prefrontal cortex cannot be identified based on gross anatomy. Schoenemann and colleagues devised a proxy measure of the prefrontal sector comprising all tissue lying in coronal slices anterior to the genu of the corpus callosum. To justify application of this segmentation scheme across phylogeny, the authors referred to cytoarchitectural maps in select species and concluded that their prefrontal proxy will underestimate values only in humans, not in other primates. However, they did not refer to existing cytoarchitectural maps of great apes[3,4], which suggest that their prefrontal measurement underestimates these species as well. The application of a topological border that does not bear a realistic correspondence to the histological parcellation of the prefrontal cortex is problematic. Because their proxy measure of prefrontal cortex underestimates the actual value to varying degrees among primates, their findings should be treated with caution.

Notwithstanding problems in their anatomical definition of 'prefrontal', even if their segmentation is accepted, it is not certain that their reported data support the conclusion that human prefrontal white matter is disproportionately enlarged. They found that human prefrontal white matter is 41% greater than that predicted for a nonhuman primate with the same non-prefrontal white matter volume. However, the slope of such scaling relationships is notoriously sensitive to the taxonomic composition of the reference group used to calculate the line[5,6]. We fit a separate regression line to the great ape data and used it to predict the individual human values. Based on our analysis, human prefrontal white matter is only 12% ± 11 (mean ± s.d.; $n = 12$) greater than allometric expectations (**Fig. 1a**). This suggests that humans have, at most, a moderate increase in prefrontal white matter volume when taking into account their phylogenetic affinities with great apes. Because great apes are the closest relatives of humans, any unique human neural specialization should be plainly apparent in comparison with this group.

Whether the volume of human prefrontal white matter departs from more general scaling trends for interconnectivity can be examined in another way. It is well established that overall neocortical white matter increases disproportionately compared with gray matter in mammals[7], either because of increased demands for connections across areas or because of increases in axon diameter. Thus, the strongest case for exceptional enlargement of prefrontal white matter would be to observe human values larger than those predicted for a primate of similar prefrontal gray matter size. We tested this idea and found that humans have only 2% ± 28 more prefrontal white matter than expected for a primate of similar prefrontal gray matter volume (**Fig. 1b**). On the basis of a prediction calculated from only great ape data, the human values are actually 17% ± 35 lower than expected. Given these results, it is difficult to make a strong claim for the evolution of specialized human enlargement of prefrontal white matter beyond

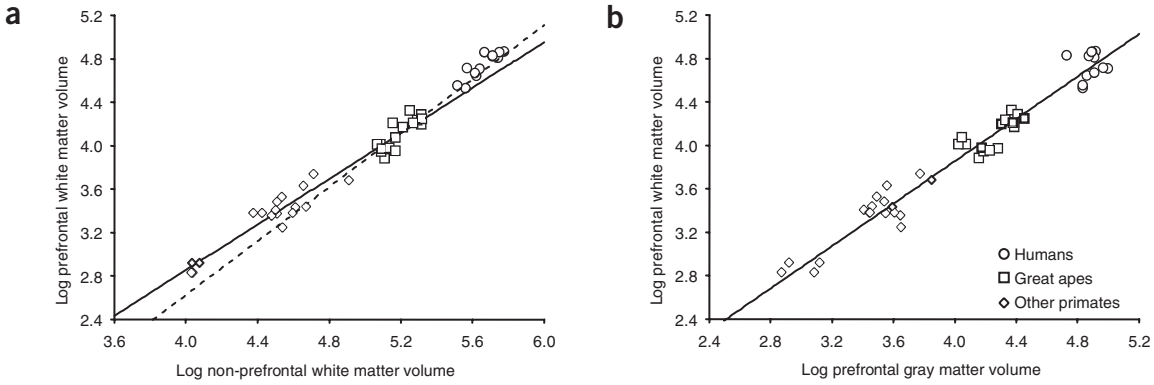


**Figure 1** The allometric scaling relationship of prefrontal white matter volume. In both plots, the least-squares regression lines are calculated based on mean values from nonhuman species, and data points are shown for reference. (**a**) Separate lines are fit to data from great apes (dashed line: $y = 1.242x - 2.344$; $r^2 = 0.777$, $P = 0.119$) and other nonhuman primates (solid line: $y = 1.049x - 1.340$; $r^2 = 0.959$, $P < 0.001$). (**b**) The line fit to all nonhuman primates is shown ($y = 0.976x - 0.049$; $r^2 = 0.977$, $P < 0.001$). The line based only on great ape data is $y = 1.110x - 0.632$; $r^2 = 0.734$, $P = 0.143$.

simple allometric scaling to maintain functional interconnectedness at a larger overall brain size. Specialization of cortical neuron types[8] and elevated gene expression associated with metabolism and synaptic plasticity[9] in humans suggest that subtle modifications of architecture, function and connectivity[10] may have been critical in the evolution of human cognitive capacities.

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**Schoenemann *et al.* reply:**

Sherwood *et al.* find the prefrontal volume proxy we used problematic, even though it has been widely used in the neuropsychological literature for many years[1–4], and it (or variants) have also been applied to non-human primates[5,6]. Sherwood *et al.* believe this proxy specifically underestimates the size of ape values, yet the frontispiece of one of the sources they cite[7] clearly shows any underestimation is minor compared to that found in humans. Taking refs. 7 and 8 together, we see that the degree of underestimation using this method increases as one gets closer to humans. An image highlighting the approximate degree of underestimation based on cytoarchitectural maps[7,8] is posted on our web site, so interested readers may judge for themselves (http://www.sas.upenn.edu/~ptschoen/Pics/prefrontal-delineation.jpg).

Furthermore, using a proxy for prefrontal volume on MRI data is exactly what Semendeferi *et al.* have reported in this same journal[9]. Their proxy was total frontal volume minus precentral gyrus volume, which also does not follow cytoarchitectural boundaries but leads to a varying degree of overestimation of prefrontal size across species. Nevertheless, the authors argue their data "...goes against the large relative differences in the prefrontal cortex between humans and great apes reported in previous publications..." (p. 274) and "... should prove useful until more definitive data become available..." (p. 273). Our proxy is no less valid; it simply focuses on more anterior regions of the frontal cortex. Together, these studies suggest that as one looks at increasingly anterior regions, humans seem increasingly disproportionate. Comparing Figures 2 and 3 from ref. 9 to our Figures 2 and 4 makes this abundantly clear.

Sherwood *et al.* believe the strongest case for specialized enlargement of prefrontal white matter would be to show that it is disproportionate relative to prefrontal gray matter. On the contrary, given that the role of the prefrontal cortex includes executive oversight of posterior regions, the interesting question is how extensively it interconnects relative to non-prefrontal regions. Our data show that the distribution of white matter is peculiar in humans, even though it scales with prefrontal gray matter.

Sherwood *et al.* also argue that great apes alone are the only valid comparison group. The problem is that only four data points can be used to estimate this relationship, thereby vastly reducing confidence in the regression prediction. (Humans would have to be more than 950% larger than predicted in order to be significantly larger.) Thus, it is an open question whether humans have more prefrontal white matter with respect to non-prefrontal white matter than great ape data predict, but it is not an open question regarding primates as a whole (at least from our data).

How humans differ from primates as a whole, versus how they differ from great apes alone, are really two different, equally important questions. Brodmann's original data show that chimpanzees have 56% more prefrontal surface area than predicted from non-prefrontal surface area. This, combined with our data suggesting an increased slope within great apes, may suggest that prefrontal elaboration accelerated in great apes.

The most interesting question is what all these patterns mean behaviorally. It is important to recognize that both behavioral selection and developmental constraint explanations exist for allometric scaling. Showing that allometry statistically explains some pattern does not indicate that it is therefore behaviorally irrelevant.

Semendeferi *et al.* note, "In a previous study, we found that the relative volume of white matter underlying prefrontal association cortices is larger in humans than in great apes"[9]. We believe our study is consistent with this statement.

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