Evolution of the prefrontal cortex: A stereological analysis of primate brain MRI scans

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Abstract:

While it is well established that the human brain is ~3 times larger than expected for a primate of our body size, there is dispute over the extent to which the prefrontal cortex (which mediates a number of behaviors thought to be important to human evolution) has increased disproportionately. Semendeferi et al. (2002, 1997) have argued that the frontal lobe (of which the prefrontal cortex is a major subcomponent) is not relatively larger in modern humans, in contrast to earlier studies dating back to Brodmann (1912).
However, Semendeferi et al. use estimates of cortical volume, whereas the earlier studies suggesting a disproportionate increase have used measures relating to cortical surface area. The volume/surface area distinction may be crucial because it appears that cortical surface area may be more behaviorally relevant than cortical volume. We measured both cortical surface area and volume using stereological techniques on a sample of primate MRI scans (obtained from the Yerkes Regional Primate Research Center; Rilling and Insel 1999) and a sample of modern humans. Both the entire cortex and prefrontal only (operationally defined as all cortex anterior to the corpus callosum) were analyzed. To avoid missing cortical surface hidden deep within sulci, surface area were estimated using the grey-white interface. A full statistical analysis of the relative differences in proportion of prefrontal cortex across primates is presented, for both volume and surface area. Preliminary indications from a subsample of chimp and human scans suggest relative increases in the anterior portions of the prefrontal in humans.

Context:

• The human brain is ~3-fold bigger than those found in our closest living relatives, but is not enlarged isometrically: some components have grown disproportionately, some have kept pace, some have lagged (to varying degrees).

• Neural tissue is evolutionarily expensive: these variations are presumably reflective of behavioral adaptation(s).

• An area of particular interest for human behavior is the prefrontal cortex: known to mediate planning, memory for serial order and temporal information, working memory, aspects of language (Broca's area), attention, social information processing.

• There are conflicting claims in the literature regarding the extent to which the human prefrontal is disproportionately enlarged.

• Studies suggesting a substantial difference tend to be surface-area-based (e.g., Brodmann 1912, Blinkov and Glezer 1968, Armstrong et al. 1991, Semendeferi et al. 2001), those that do not tend to be volume-based (e.g., McBride et al. 1999, Semendeferi et al. 1997, 2002; note also that Semendeferi et al. measure the entire frontal cortex rather than just the prefrontal because of the difficulties of delineating prefrontal on MRI scans).

• Cortical surface area appears to scale almost isometrically with brain volume: it does not follow the surface/volume scaling relationship for objects differing only in size (Jerison 1982). This suggests that surface area may be more functionally important that volume per se.

Question driving the study:

Do surface area measures of the prefrontal show larger human/non-human differences than volumetric measures on the same subjects?

Methods:

A series of primate brain scans were obtained from Yerkes Regional Primate Research Center (these have been the subject of previous analyses: Rilling and Insel 1999). The non-human primate species included in this study were: 2 *Cercocebus torquatus atys* (sootey mangabey), 3 *Macaca mulatta* (rhesus macaque), 6 *Pan troglodytes* (chimpanzee), and 4 *Pan paniscus* (bonobo). These scans were T1 weighted, TR=19·0 ms, TE=8·5 ms, slice thickness=1·2 mm, slice interval=0·6 mm, spatial resolution was 0·70 mm2.

Homo sapiens brain scans comprised a sample of 6 healthy young female individuals (18-45 years old). These scans were also T1-weighted, with TR=32 ms, TE 8 ms, slice thickness=1.5 mm, spatial resolution of .94 mm2. Approval was obtained from the human subjects committee at U.C. San Francisco where the scans were obtained.

Brains were processed as follows:

1) Primate brains were corrected for magnetic field inhomogeneities (which can cause fluctuations in average intensity across slices). Human scans did not display obvious inhomogeneities and so were not processed with this step.

2) Cortices were semi-manually extracted using flood-fill thresholding techniques.

3) Cortices were aligned to anterior commissure – posterior commissure orientation.

4) Grey and white matter regions were segmented using FAST (FMRIB's Automated Segmentation Tool, see http://www.fmrib.ox.ac.uk/fsl/). This method implements a hidden Markov random field model and an associated Expectation-Maximization algorithm. Compare figure 1 (greyscale image) to figure 2 (tissue segmented on the same slice into one of 3 classes: CSF – dark grey, grey matter – light grey, white matter – white)

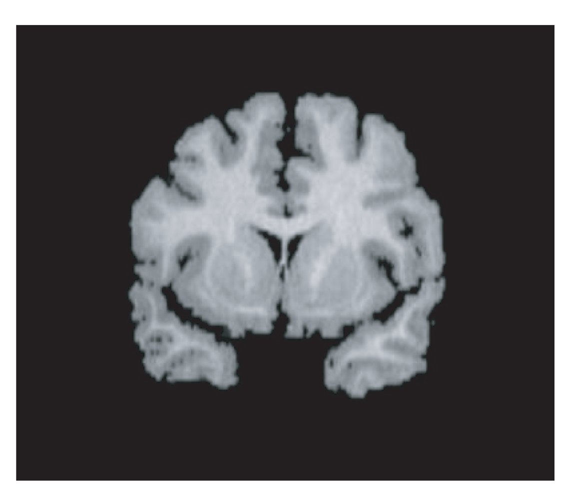

Figure 1

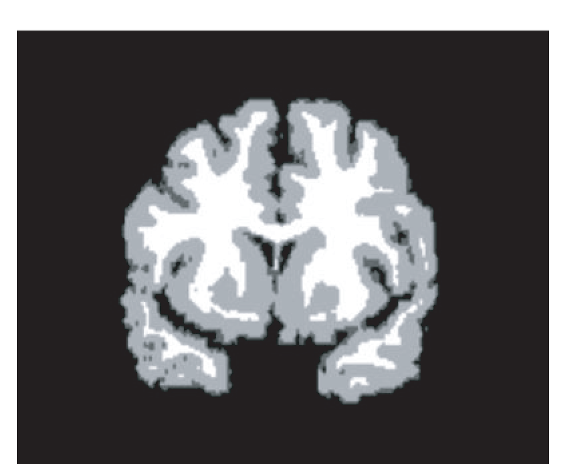

Figure 2

5) Stereological methods (as implemented by Analyze Image Processing software; details in Roberts et al. 2000) were used to estimate both volume and surface area of brains in coronal orientation. Stereology involves counting intersection points between a randomly-aligned grid overlain on the image and key points of interest on that image. Volume is calculated by multiplying the number of intersection points by constants that take into account slice thickness and area associated with each intersection point. Surface-area-per-unit-volume is can be estimated as:

2x(the number of intersections of the 3D grid on the surface of interest) x (total length of the grid lines)

Total surface area is then calculated by multiplying surface-area-per-unit-volume by total volume. The method is robust to large differences in grid size, but nevertheless grid size was chosen separately for each species such that the total number of intersection points was a minimum of 10,000. Figures 3, 4 and 5 show the intersection points (green) for the three orthogonal directions on a single slice of prefrontal cortex. Because point values vary slightly depending on the orientation of the grid, 10 randomly chosen grid alignments for the XY dimension were chosen for each subject for each measurement, and results were averaged (within subject and measurement).

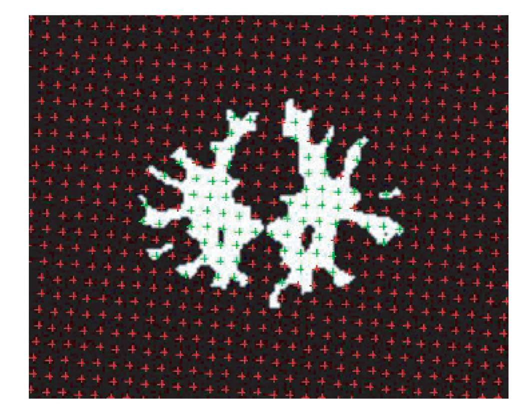

Figure 3

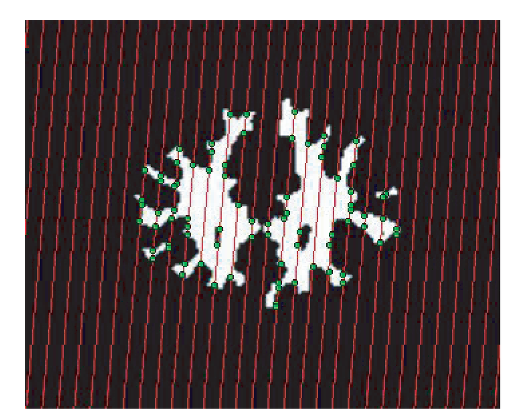

Figure 4

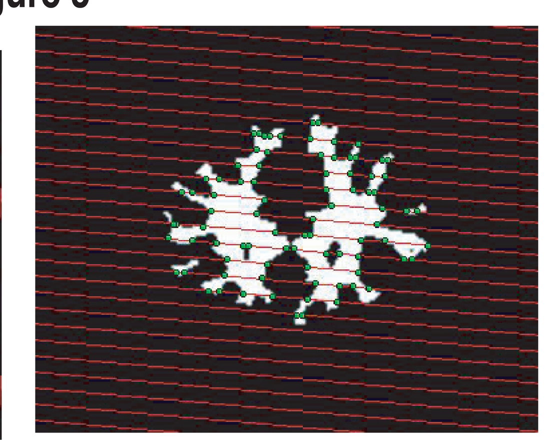

Figure 5

Because prefrontal cortex is difficult to delineate unequivocally on MRI scans, it was operationally defined in this study as all tissue anterior to the genu of the corpus callosum (figures 6 and 7 depict the prefrontal cortex highlighted in red in a macaque and human specimen respectively). Surface area stereology was performed on the white matter segmentation, to avoid missing surface hidden deep within sulci. Area of the face of the last slice of prefrontal was subtracted from the stereological estimate of prefrontal surface area (since this flat surface is included by default in the initial stereological estimate of the surface area of the prefrontal portion as described above).

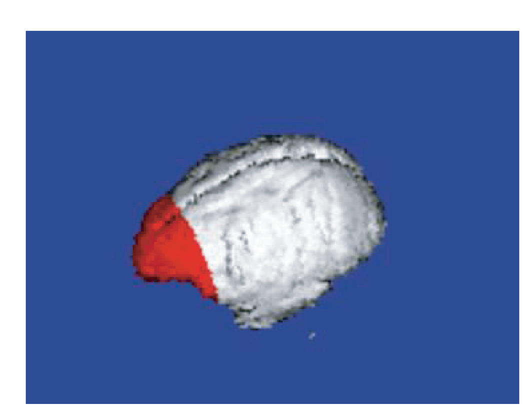

Figure 6

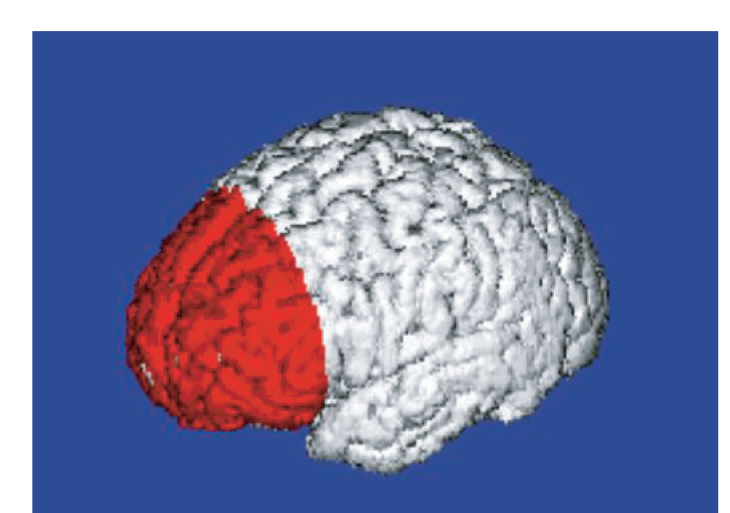

Figure 7

Results:

The means, standard deviations, and ranges for surface area and volume are summarized in tables 1 and 2.

Expressed as percentage of total cortex, human prefrontal cortical surface area is not larger than human prefrontal cortical volume (at least as we have operationally defined prefrontal in this study), and in fact is slightly smaller (compare figures 8 and 9).

However, humans do have a greater percentage of prefrontal volume and surface area than the other species measured in this study. These differences are statistically significant ($p<.03$) except for the surface area comparison between Homo sapiens and Pan troglodytes.

The limited number of species sampled in this study suggests that prefrontal cortical volume increases disproportionately fast compared to the rest of the brain.

While the human cortical volume is 3.4 times larger than the average of chimp and bonobo, the human prefrontal volume is 4.6 times larger (the corresponding values for surface area measures are 2.1 and 2.8). Thus, these data do support the contention that the human prefrontal has undergone a disproportional increase.

However, this appears to be an allometric trend (figures 10 and 11). Human prefrontal values are predicted by the size of our cortex, using trends established in the non-human specimens in this study. Note that prefrontal cortex shows significantly positive allometry: prefrontal cortex increases faster than the rest of the brain (cf. Holloway 2002). Note that this may nevertheless still have important behavioral implications.

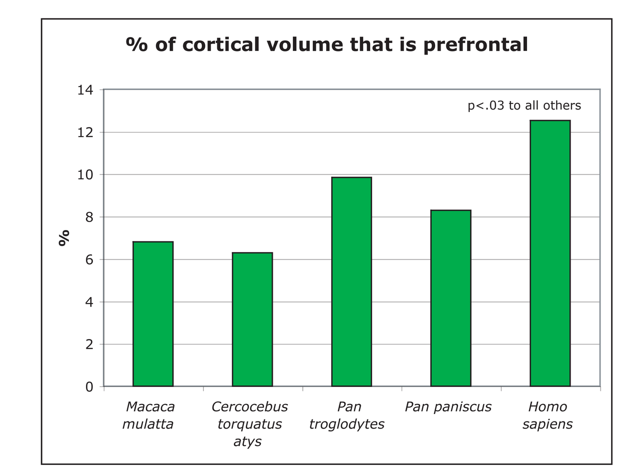

Figure 8

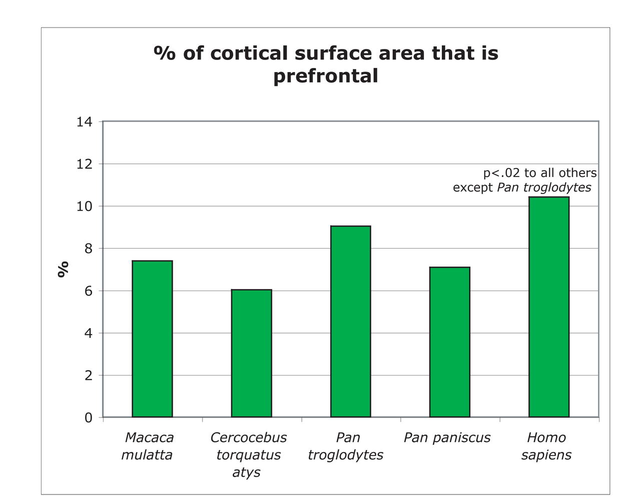

Figure 9

Table 1

	total cortical volume (mean ± SD in cm^3)	prefrontal cortical volume (mean ± SD in cm^3)	total cortical surface area (mean ± SD in cm^2)	prefrontal cortical surface area (mean ± SD in cm^2)
Macaca mulatta	69.0 ±4.7	4.7 ±.5	248.3 ±18.0	18.3 ±3.4
Cercocebus torquatus atys	84.4 ±5.3	5.3 ±.6	302.5 ±5.5	18.2 ±1.4
Pan troglodytes	277.8 ±27.9	27.9 ±7.5	819.0 ±79.0	74.9 ±17.9
Pan paniscus	284.2 ±23.6	23.6 ±6.3	795.9 ±167.8	57.2 ±18.1
Homo sapiens	947.1 ±118.8	118.8 ±18.9	1790.3 ±173.1	185.9 ±26.6

Table 2

	total cortical volume (cm^3)		prefrontal cortical volume (cm^3)	
	min	max	min	max
Macaca mulatta	63.2	75.2	4.3	5.3
Cercocebus torquatus atys	81.9	86.9	4.9	5.7
Pan troglodytes	236.8	334.6	19.0	41.4
Pan paniscus	240.8	385.0	19.4	32.9
Homo sapiens	866.6	1098.9	91.9	136.2

	total cortical surface area (cm^2)		prefrontal cortical surface area (cm^2)	
	min	max	min	max
Macaca mulatta	228.5	263.5	16.1	22.3
Cercocebus torquatus atys	298.5	306.4	17.2	19.2
Pan troglodytes	710.0	941.7	55.8	102.2
Pan paniscus	665.9	1041.7	43.5	83.9
Homo sapiens	1601.2	2067.5	148.7	214.5

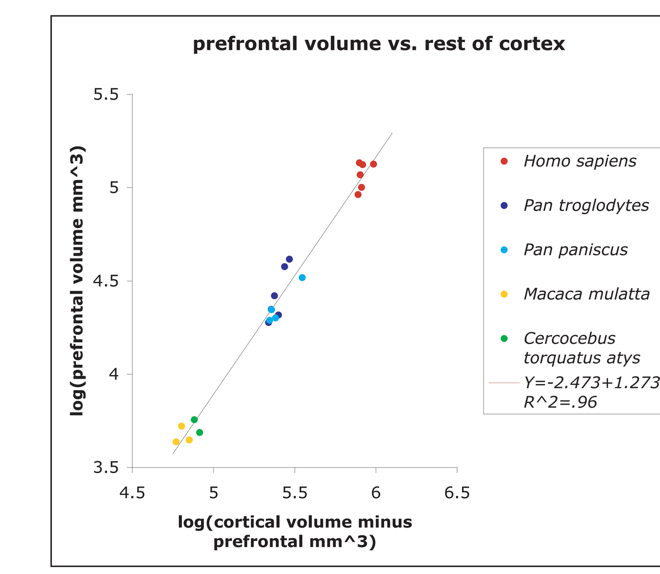

Figure 10

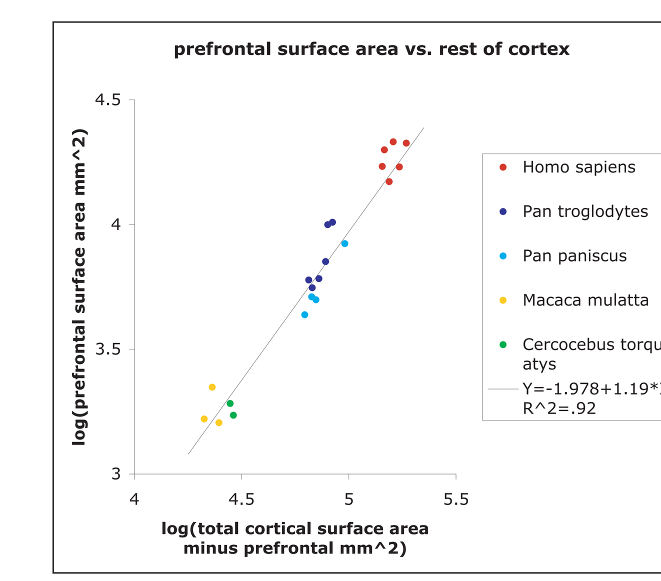

Figure 11

Conclusions

• The conflicting reports in the literature regarding the size of human prefrontal cortex do not seem to be explained by the surface area/volume distinction.

• The human prefrontal is disproportionately large, though this appears to be the result of an allometric trend

• Prefrontal cortex increases significantly faster than the rest of the brain across the species studied here.

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Drs. James Rilling and Thomas Insel kindly agreed to give us copies of their primate brain scans, without which this study would of course not be possible. Stephanie Langin-Hooper and Piper Silverman helped with data processing. We also thank the human subjects who's scans we used for this study.

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