

Brain Size and Folding of the Human Cerebral Cortex

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During evolution, the mammalian cerebral cortex has expanded disproportionately to brain volume. As a consequence, most mammals with large brains have profusely convoluted cortices. The human cortex is a good example of this trend, however, given the large variability in human brain size, it is not clear how cortical folding varies from the smallest to the largest brains. We analyzed cortical folding in a large cohort of human subjects exhibiting a 1.7-fold variation in brain volume. We show that the same disproportionate increase of cortical surface relative to brain volume observed across species can be also observed across human brains: the largest brains can have up to 20% more surface than a scaled-up small brain. We introduce next a novel local measure of cortical folding, and we show that the correlation between cortical folding and size varies along a rostro-caudal gradient, being especially significant in the prefrontal cortex. The expansion of the cerebral cortex, and in particular that of its prefrontal region, is a major evolutionary landmark in the emergence of human cognition. Our results suggest that this may be, at least in part, a natural outcome of increasing brain size.

Keywords: brain size, cortical folding, development, evolution

Introduction

The human brain is distinctively larger than that of any other primate, mainly due to the great expansion of the cerebral cortex (Rakic 1995). Given its volume, however, this expansion is not completely unexpected. The volume of the brain and the area of its cortical surface are strongly correlated across many mammalian species (Prothero and Sundsten 1984). When brain volume and cortical surface area are plotted in a logarithmic scale, widely different species ranging in size from tree shrew to elephant tightly follow the regression line (Prothero and Sundsten 1984). If brains were just scaled-up versions ones of the others, the slope of this regression line should be of 2/3, which is the slope of a simple scaling of surface with volume. The observed slope of 0.91 signals a disproportionate expansion of the cerebral cortex in relation to brain volume, which makes the cortex of most mammals with a large brain, such as humans, profusely folded (Welker 1990). Indeed, a strong link between cortical growth and folding has been revealed experimentally in mutant mice (Kuida et al. 1996; Haydar et al. 1999; Chenn and Walsh 2002) and put forward theoretically as a major cause of cortical folding (Toro and Burnod 2005).

Surprisingly, analyses of the relationship between the degree of folding and brain size within humans have not show any significant correlation, even in presence of considerable variations in brain volume. Zilles et al. (1988) studied the

degree of folding in a cohort of 61 subjects, covering a 1.5-fold variation in brain volume. No correlation was observed between the degree of folding and brain volume, nor with age, body weight, body length or brain weight. There were no significant differences in the degree of folding neither between gender nor between hemispheres. Using a larger cohort ($N = 94$), Zilles et al. (1997) again did not found significant gender differences, but were able to observe a slightly higher degree of folding in the male left hemisphere compared with the right hemisphere.

It is possible, however, that if variations in cortical folding were regional, using a single global value to estimate the degree of folding, as was done by Zilles et al. (1988, 1997), may mask these differences. In the recent work of Luders et al. (2004, 2006), for example, significant gender differences in the folding of the prefrontal and parietal regions were found in a group of 60 subjects (30 males and 30 females) after parceling the cortex into several regions (Luders et al. 2004), or using a local measure of gyrification (Luders et al. 2006). Indeed, when estimations of cortical folding were computed along the rostro-caudal axis, Zilles et al. (1988, 1989) were able to show the presence of a gradient in the degree of folding of primates, and in particular, a higher degree of folding of the human prefrontal cortex compared with that of any of the other primate species under study.

Here we present an analysis of the variations in cortical surface area and degree of folding carried out in a large cohort of human subjects ($N = 314$), with a substantial 1.7-fold variation between the smallest and the largest brain volumes. We introduce a local measure of cortical folding, the surface ratio, based on the computation, at every point of the cerebral cortex, of the amount of cortical surface packed in a limited spherical volume centered around that point. We observed a disproportionate increase in cortical surface area with brain size, similar to that observed across species, and a specific increase in the degree of folding of the prefrontal cortex in the larger brains. Our results suggest that, at least in part, the global increase in cortical surface area and the high degree of folding of the prefrontal cortex that distinguishes the human brain from that of other primates (Zilles et al. 1988; Rilling 2006), may be a consequence of its global increase in volume during evolution.

Methods

Neuroimaging

Structural magnetic resonance images of the brain were obtained for 408 adolescents 12 to 20 years old recruited in the Saguenay Youth Study (Pausova et al. 2007). Magnetic resonance imaging data volumes were collected on a Phillips 1.0-T superconducting magnet.

High-resolution anatomical T_1 -weighted images were acquired using the following parameters: 3-dimensional RF-spoiled gradient echo scan with 140–160 sagittal slices, 1-mm isotropic resolution, time repetition = 25 ms, time echo = 5 ms, flip angle = 30° . Surface reconstructions of the cerebral cortex were obtained using FreeSurfer (Dale et al. 1999). For every subject, FreeSurfer segments the gray matter, the white matter and other subcortical structures, and then computes triangular meshes that recover the geometry and the topology of the pial surface for the left and right hemispheres. Finally, FreeSurfer establishes a correspondence between the cortical surfaces across subjects using a nonlinear alignment of the principal sulci in each subject's surface with an average surface (Fischl et al. 1999). In our analyses we used the subsample of 314 subjects, 164 females (183.5 ± 24.3 months of age) and 150 males (183.6 ± 22.5 months of age), for whom we were able to compute cortical thickness reliably. As shown in Figure 1, there was no significant change of total surface area ($P = 0.10$) nor of total hemispheric volume ($P = 0.70$) with age.

Cortical Folding

In the past, the degree of folding of a brain has been estimated by comparing the area of the cortical surface to the area of its external surface (Elias and Schwartz 1969). An alternative approach has been to compute the ratio between the pial contour and the outer contour in successive coronal sections (Zilles et al. 1988, 1989; Armstrong et al. 1995), which allows one to study rostro-caudal variations in folding. We extended these ideas to obtain a local estimate of the degree of cortical folding. We measured, for every point x on the cortical surface, the area $C_{x,r}$ contained in a small sphere of radius r centered at x , $S_{x,r}$ (see Fig. 2). If the brain were lissencephalic, the area inside the sphere $S_{x,r}$ would be approximately that of the disc $D_r = \pi r^2$. We estimated the local degree of folding through the surface ratio $SR_{x,r}$

$$SR_{x,r} = \frac{C_{x,r}}{D_r}$$

The sphere has to be sufficiently large as to encompass a few folds, but small enough to make the approximation of the lissencephalic area reasonable. In our analyses, we used $r = 20$ mm, but our findings remained the same for $r = 15$ mm or $r = 25$ mm (Fig. 5). A fast implementation of this method in standard C can be obtained at <http://brainfolding.sourceforge.net>.

Statistical Analyses

In order to study the effect of total cortical surface on local folding, an F -ratio map was computed by comparing the variance explained by a model including intercept, total hemispheric volume and surface with that explained by a partial model excluding the effect of surface (Fig. 4b). Total volume is included in the multiple regression because, although strongly correlated with surface, its effect on folding is the opposite: folding increases with surface if the volume is constant, but decreases with volume if the surface is constant. The significance threshold was set to $P = 0.01$, and corrected for multiple comparisons using the False Discovery Rate method (Genovese et al. 2002), yielding a cut-off value of $F_{2,311} = 9.2$.

Results

Scaling of Cortical Surface with Hemispheric Volume

Figure 3 shows the relationship between cortical surface and hemispheric volume of the subjects in our study plotted in a log-log graph. The slope of the regression line is 0.85, higher than the value expected for simple scaling (closer to $6/7$ than to $2/3$; this difference is significant with $F_{1,312} = 98.1$, $P < 0.001$), and similar to the value of 0.80 obtained by Rilling and Insel (1999) for the scaling between cortical surface and brain volume across different primate species.

This shows that, compared with the smaller human brains, the larger brains tend to have more cortical surface than what

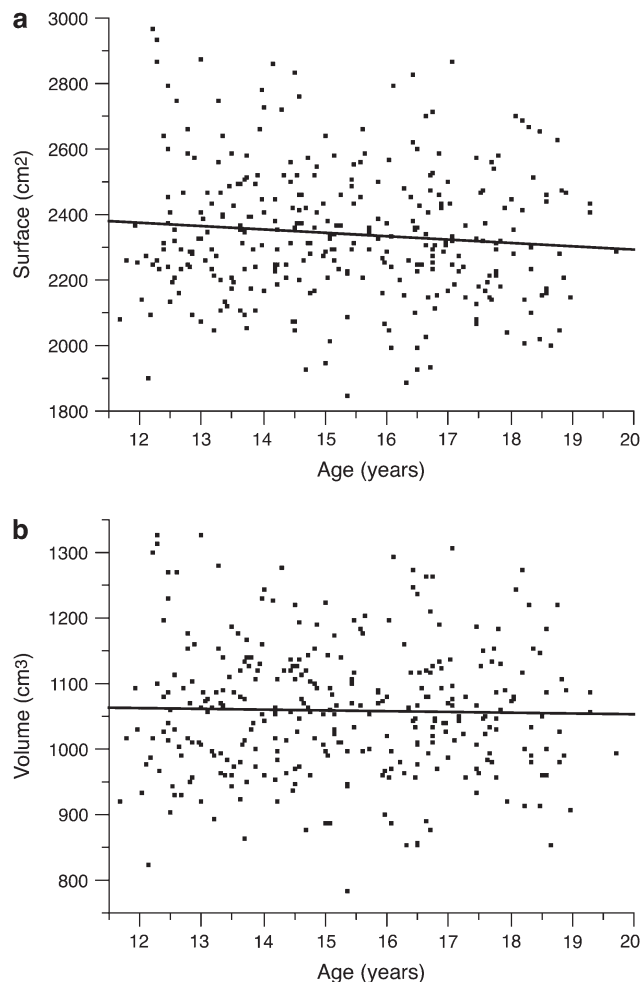


Figure 1. Changes in total hemispheric surface and total hemispheric volume with age. There was no significant correlation between (a) total surface area ($P = 0.10$) nor of (b) total hemispheric volume ($P = 0.70$) with age.

would be expected for their volumes. Indeed, if 1 of the largest brains in our sample were resized to match the volume of the smallest brains, its surface would be up to 20% larger. Although in most cases larger brains are more folded than smaller ones, it is not the cortical surface or brain volume alone that determine the degree of folding, but their relative proportion. The shaded bands in Figure 3 have each a slope of $2/3$ and show groups of brains with similar degree of folding. Cutting across the bands, one can see that even a brain of average volume can have a high degree of folding. This is more frequently the case, however, for large brains.

Average Cortical Folding

In different human and nonhuman primates, the degree of cortical folding has been shown to follow a rostro-caudal gradient (Zilles et al. 1988, 1989). This type of gradient has been also described during early human development (Armstrong et al. 1995). Furthermore, as we noted previously, the difference in the degree of folding between human and nonhuman primates is greater in these rostral cortical regions compared with the caudal regions (Zilles et al. 1988).

We estimated the local degree of folding by evaluating, for every point on the cortex, the ratio between the pial surface

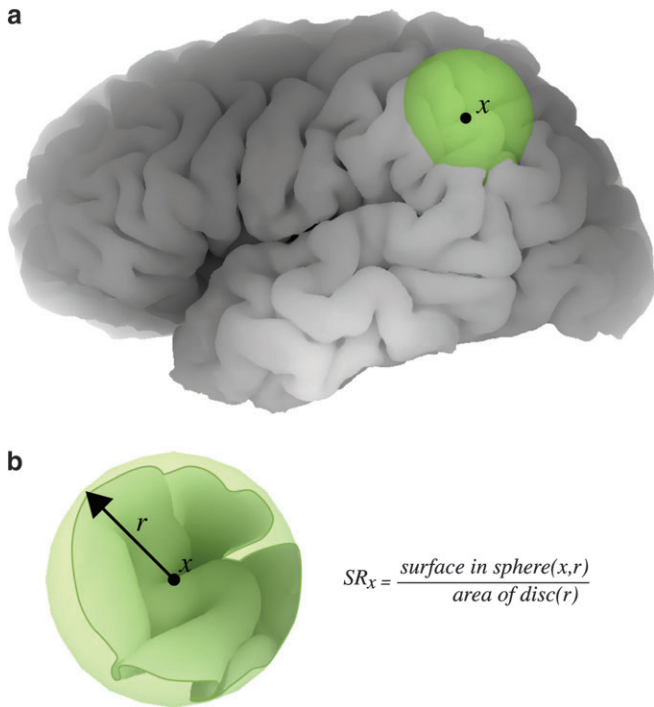


Figure 2. Surface ratio for the local estimation of folding. For every point x in the cortex (a), the local folding is estimated through the ratio between the pial surface contained in a small sphere around the point and that of a disc of the same radius r (b). The disc approximates the area of that region if it were not folded. Sphere radius = 20 mm.

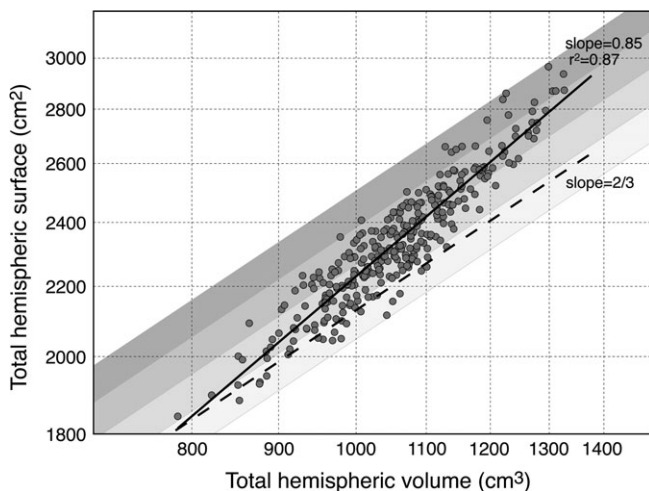


Figure 3. Cortical surface versus hemispheric volume (log-log graph). The slope of the regression line for geometrically similar brains should be of $2/3$ (dashed line). The actual slope of 0.85 (solid line) indicates that larger human brains have disproportionately more surface than the smaller. The shaded bands, with slope of $2/3$, show brains with similar surface-to-volume ratio. The amount of surface relative to volume increases as we move from the lighter, to the darker bands.

contained in a small sphere and that of a disc of the same radius, which approximates the surface area of that region if it were not folded (see Methods). We refer to this measure as the “surface ratio”. Figure 4a shows a map of the average surface ratio generated from the 314 left cortical surfaces in our dataset. This map reveals a rostro-caudal gradient of cortical

folding, with higher folding occurring in the caudal part of the brain. The same gradient was observed in the right hemisphere, and for 3 different sphere radii (Fig. 5).

The gradient in Figure 4a is consistent with the results of previous studies and shows that a sphere of fixed size will pack, on average, more cortical surface in the occipito-parietal regions than toward the frontal and temporal poles.

Regional Folding in Relation to Brain Size

We used multiple regression to fit the local values of the surface ratio in a linear model taking into account the total hemispheric surface and the total hemispheric volume. Figure 4b shows the significance of the effect of total hemispheric surface on local folding as an F -ratio map. As expected, the degree of folding correlates significantly with total surface almost everywhere in the cortex. The strength of this effect, however, varies regionally and is particularly significant in the prefrontal cortex.

By comparing Figure 4a and b we can see that brains with larger cortical surface relative to hemispheric volume increase their folding especially in the regions that showed, on average, the least folding.

Discussion

When brains are compared across species, it is possible to observe a disproportionate increase in cortical surface area with brain volume and, if humans are compared with other primates, this increase in folding is particularly significant in the prefrontal cortex (Zilles et al. 1988). Here we have shown that both patterns can be also observed within human subjects.

The prefrontal cortex is involved in various high-level cognitive functions (Goldman-Rakic 1996; Wood and Grafman 2003; Petrides 2005), and its expansion has been regarded as a major evolutionary modification leading to the emergence of human intelligence. Two main views exist concerning the way in which evolution may achieve this kind of modification. The first highlights the global coordination in the expansion of different brain regions, suggestive of a very conserved developmental mechanism shared across species (Finlay et al. 2001). The second, known as the mosaic evolution hypothesis, emphasizes a selective, species-specific expansion of independent structural and functional modules (Barton and Harvey 2000). The expansion of the human prefrontal cortex has been regarded as an example of such specific selection, in humans, of the cognitive functions supported by the prefrontal cortex (Rilling 2006).

If the structure of the brain of a particular species were determined by the evolutionary selection of specific modules, then the proportion of the volume of these modules in all members of the same species should be the same (Barton and Harvey 2000). This would not be the case, however, if the proportion of different brain structures changed as a function of brain size. In the latter case, and due to the intraspecies variability in brain size, we should be able to observe within the same species structural variations similar to those observed across species. Our results support this latter possibility, and suggest that the increased degree of prefrontal folding may be, at least in part, a consequence of the increased brain size. It is unclear, however, what mechanisms may underlie the relationship between brain size and cortical folding. Although cortical growth alone plays certainly a major role in the formation and

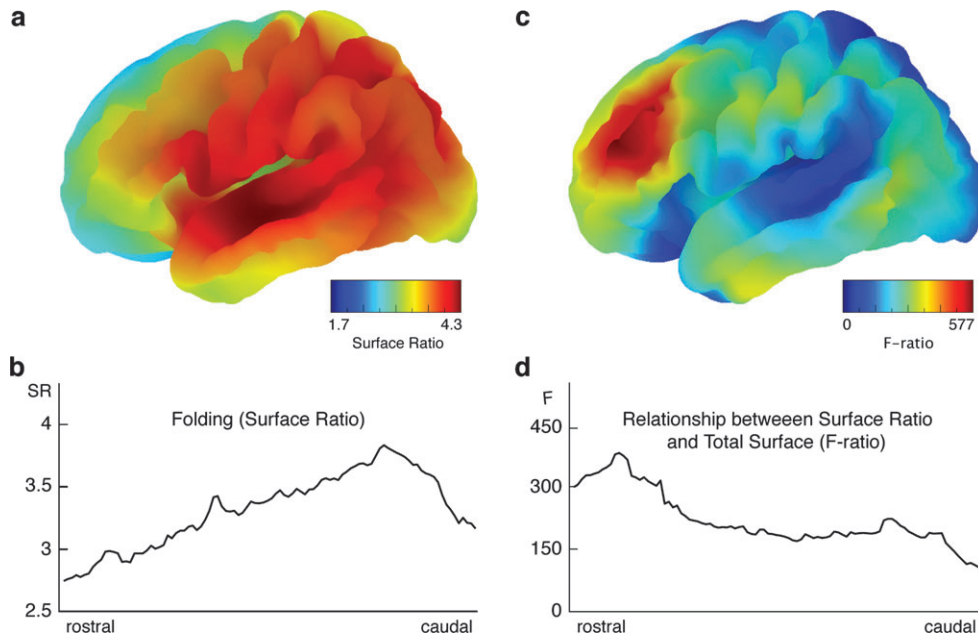


Figure 4. Map of average cortical folding (surface ratio) and significance of the effect of total cortical surface on local folding (F -ratio values). (a) The local folding shows a rostral-caudal gradient, with the least folded regions situated toward the rostral part of the brain, and the more folded regions located toward the caudal part. (b) Rostro-caudal profile of folding estimated through the surface ratio. (c) The degree of folding varied with total cortical surface, the most significant effect, and the strongest correlations, being found in the prefrontal cortex. (d) Rostro-caudal profile of the F -ratio.

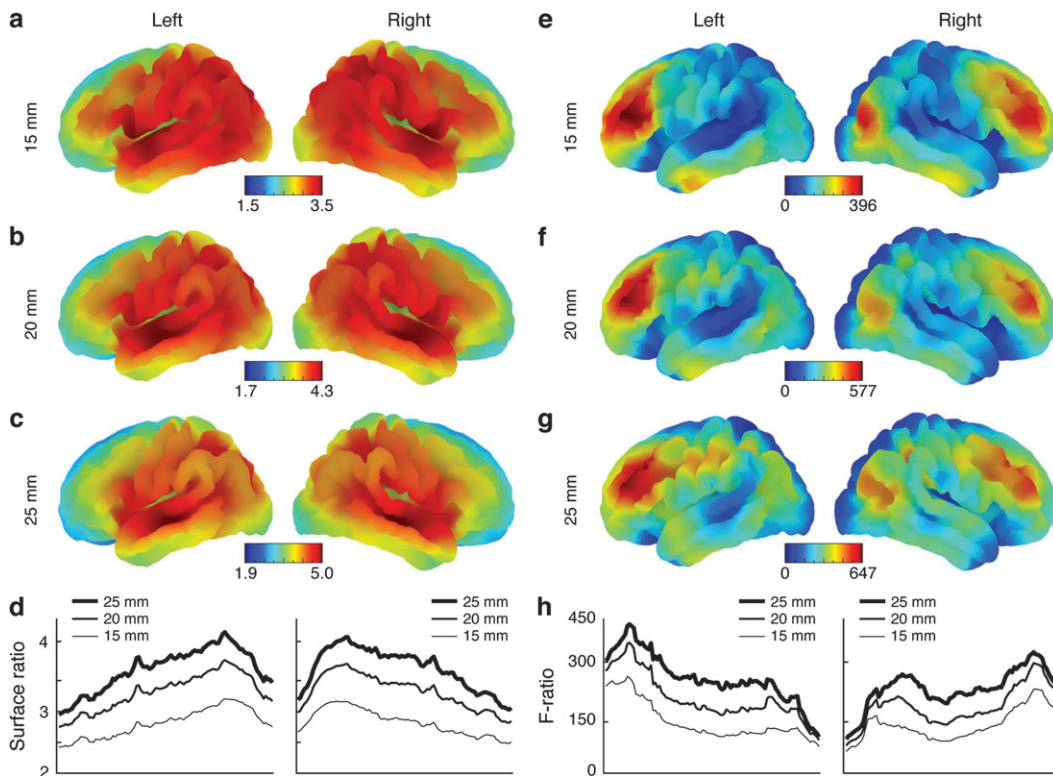


Figure 5. Effect of sphere radius length. The rostro-caudal gradient in the degree of folding, and the prefrontal effect of total cortical surface on folding, are the same for surface ratios computed with a sphere-radius of 15 mm (a, e), 20 mm (b, f), and 25 mm (c, g). (a–c) Average folding map. (e–g) Effect of total cortical surface on folding. (d) Rostro-caudal profile of average folding. (h) Rostro-caudal profile of statistical significance (F -ratio).

deepening of cortical folds (Kuida et al. 1996; Haydar et al. 1999; Chenn and Walsh 2002; Toro and Burnod 2005), several other processes may be involved, such as a differential expansion of superior and inferior cortical layers (Richman

et al. 1975; Kriegstein et al. 2006), a differential growth of the progyral versus the prosulcal regions (Welker 1990) or variations in the pattern of cortico-cortical connections (Van Essen 1997; Hilgetag and Barbas 2006).

The increase in brain size is one of the most evident features of human brain evolution. Among mammals, primates have particularly large brains in relation to body size, and humans have the largest brains among all primates (Jerison 1973; Passingham 1973). Genes involved in the regulation of brain size seem to be among the fastest evolving in primates, and especially in the lineage leading to humans (Dorus et al. 2004; Vallender and Lahn 2006). In humans, nonfunctioning mutations of some of these genes, Microcephalin, Abnormal Spindle-like Microcephaly-associated, and Sonic Hedgehog, cause different types of microcephaly—a severe reduction of total brain size to levels typical of great apes or Australopithecines, accompanied by an overall simplification of the folding pattern (Gilbert et al. 2005).

The increase in prefrontal folding with brain size may be another aspect of the link between the size of different brain structures and their time of development during ontogenesis (Finlay and Darlington 1995; Finlay et al. 2001). By analyzing the volume of different brain structures across species, Finlay and Darlington (1995) observed that the rostral telencephalic structures exhibit the steepest increase in volume relative to body size. The more caudal structures of the rhombencephalon start their development earlier than rostral structures such as the cerebral cortex, which take also longer to reach maturation. It is possible that the differences in prefrontal folding that we observed, and perhaps also those observed among primates, can be a consequence of the prolongation of this rostro-caudal gradient into the cerebral cortex. This idea is supported by the fact that human gyrification lasts up to 1 month longer in the rostral than in the caudal regions of the cerebral cortex (Armstrong et al. 1995).

Under the hypothesis of mosaic evolution, the greater elaboration of the prefrontal cortex in humans may be seen as resulting from the selection of the cognitive functions it supports. It is also possible, however, that the availability of more cortical surface leads to the further specialization of this region by allowing a larger elaboration of the corresponding cytoarchitectonic fields or the emergence of new cytoarchitectonic structures, which may then support the refinement of its associated functions. Brodmann's area 10, which occupies a large part of the prefrontal cortex, is indeed greatly expanded in humans compared with other primates (Semendeferi et al. 2001; Allman et al. 2002; Jerison 2006), and spindle neurons, a type of neuron in the anterior cingulate cortex unique to humans and great apes, appear to relay especially to area 10 (Allman et al. 2002). The coordinated expansion of functionally related structures, such as the medial nuclei of the thalamus, should also follow from the enlargement of the prefrontal cortex. Experiments showing the plasticity of the brain in cases of enucleation (Rakic 1988), rewiring (Pallas 2001) and surgically reduced cortices (Huffman et al. 1999) provide striking examples of this type of coordinated adaptation of functionally related structures.

The cranial volume of the *Homo* genus has more than doubled during the 2 million years that separate us from *Homo habilis*, and the cortical surface may have expanded at least in the same proportion. Our results suggest that this growth should lead to a natural expansion of the prefrontal cortex. This expansion may have allowed for the greater specialization of the cortical regions related today to goal-directed sequential behavior (planning) and divergent (creative) thinking, and may have been a key process for the emergence of human cognition.

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Notes

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