Supporting Information

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SI Methods

In what follows we describe a very simple model for the folding of the cortex. In this model the cerebral cortex is considered to be a folded GM surface of constant thickness and regular folding pattern surrounding a regularly folded WM volume or a region-specific or species-specific deformation thereof that preserves A_W, V_W, and V_G relative to the idealized model. The volume of the WM and the surface area of the GM–WM interface are determined by the amount of axonal volume and total cross-sectional area needed for a given connectivity with neuronal soma in the GM. We also assume that the average number of nonneuronal cells in the WM per unit axon length is constant across species, a hypothesis that is supported in the literature (1).

Beyond these assumptions, we specifically do not take into account detailed functional or anatomical information about the cortical structure, because we are interested in properties (such as scaling laws) that are common to primate brains varying in size by a factor of 10,000. As can be seen in the text of the paper, by using this model one can estimate the scaling laws of various quantities that cannot be directly measured (such as average axon cross-sectional area and GM neuron connectivity), and at the same time the validity of the model can be tested by comparing its prediction of the relationship between the WM and GM's folding indexes, which can be directly measured to empirical data.

The Average Axon Length. White matter is largely composed of axons connecting neurons in gray matter, along with the glial cells that support their function. The volume of each axon is simply its cross-sectional area times its length. If there is no significant correlation between these two latter quantities, then the total axonal volume is the average axon cross-section area a, times the average axonal length l, times the total number of axons (given by the number of GM neurons, N, times the fraction of such neurons connected by a myelinated axon in WM, n). The total glial cell volume is well approximated by the number of nonneuronal cells, O, times the average WM nonneuronal cell volume, v_0. Thus,

$$V_W = nNal + Ov_0.$$

Note that we neglect the contribution to the volume of the (small) number of neuronal cells in WM and of axons not originating or terminating at the GM.

Experimentally, it can be shown that V_W can be obtained as a power law of either N or O ($V_W \propto N^{1.1}$ and $V_W \propto O^1$). In the latter case, and in view of the formula above, the fact that WM volume increases linearly with O means that the average non-neuronal cell volume in WM remains approximately constant for all primates, in line with our previous results (2). Furthermore, it can also be shown (see ref. 3 for details in a slightly different context) that for the relation between V_W and O (or N) to be expressed as a power law, the ratio between the volumes of axonal and nonaxonal matter in the WM must also remain constant. We can then write

$$V_W = rnNal$$

(where r is a constant ratio between axonal volume and V_W). If we assume further that the nonaxonal WM is homogeneously distributed, then any given cross-sectional area of axons will be embedded according to the same fixed ratio k to the surrounding nonaxonal matter. The GM–WM interface area will therefore be given by

$$A_W = 2.r.n.N.a/p.$$

The factor p, assumed to be constant, is the weighted (by cross-sectional area) average value of cos θ, θ being the incidence angle of each axon into the GM–WM interface. Thus, the average length of the WM axons is

$$l = 2.V_W/(p.A_W).$$

Note that an economically built brain (i.e., one folded only as much as it needs to be to accommodate all its WM axons as tightly packed as possible) would have $p \approx 1$. In any case, $p = <1$, so V_W/A_W can always be taken as a lower bound for l.

Other than the constants r and p, the only parameters describing the overall structure of the WM that have not been directly measured or estimated are n and a, respectively the fraction of neurons in GM with myelinated axons in WM and the average cross-sectional area of myelinated axons in WM. Note, however, that in all formulas above they figure only as the product $n.a \propto A_E/N$. To obtain the individual scaling rules, one further assumption must be made.

Scaling of Average Axon Cross-Sectional Area. The average cross-sectional area a of myelinated axons in the WM can be estimated on the basis of the assumption about the proportionality between L and O. Considering that $V_W \propto n.N.a.l$, we get that $a \propto V_W/L \propto V_W/O$. Because we show that $V_W \propto O$, it follows that V_W/O is constant, that is, that a is approximately invariant for primate brains. The same relationship holds if we consider O to be proportional to total axonal surface S, rather than length. To see that relationship, consider axons with constant cross-sectional areas and diameters, such that the total axonal surface is $S \propto La^{1/2}$. It still holds that $a \propto V_W/L$ (from the model) and that $V_W \propto O$ (empirically). If we now assume $O \propto S$, then $a \propto S/L \propto a^{1/2}$. Thus, $a^{1/2} \propto$ constant. This result in turn implies that O is again proportional to L, and thus the scaling law for n remains the same.

Cortical Folding and Connectivity. Extending the model we introduced above, we now show that the folding index for the surface of the cortex, F_G, is uniquely determined by the value of the folding index of the WM–GM interface, F_W. As we argue in the text, the axonal connectivity parameters (the total axonal length and total axonal cross-sectional area) in the WM determine the amount of folding of the WM–GM interface, which in turn shapes the folding on the cortical surface.

We start by dividing the total cortical surface A_G into two parts: the smooth exposed surface A_E and the convoluted sulci surfaces emanating from the surface and burrowing toward the WM, with total area ΔA_G (Fig. S1). Because by definition $F_G = A_G/A_E$, then

$$\Delta A_G = A_E(F_G - 1).$$

We also divide the WM–GM interface area into two parts: an inner core that is reasonably smooth (like the exposed area of the cortex), with surface area A_{W0} (the area of a sphere with volume V_w), and the anti-sulci penetrating the GM, with total surface area ΔA_W.

Assume now that the exposed cortical surface is, to a good approximation, an isometrically scaled-up copy of the inner WM core. Then the ratio between their respective surface areas will be given by the square of the ratio between their characteristic lengths. Thus,

$$A_{W0} = A_E(R_W/R)^2.$$

We assume, for the sake of simplicity, that GM thickness T does not vary significantly between neighboring gyri and that the total cortical area A_G is simply the total exposed cortical area A_E (the area of the exposed gyri) plus the area inside each sulcus. Then s will be the ratio between the cortex radius R and the radius of what remains once the GM is removed. But the thickness of the folded layer of GM is clearly $h + T$, where h is the average depth of the sulci. Thus, $R_w = R - h - T$. Furthermore, by the uniformity hypothesis, the average distance between adjacent sulci is $2T$. Thus, the total area A_G is given by $A_G = A_E + A_E h/T$. The folding index $F_G = A_G/A_E$ is then $F_G = 1 + h/T$ [it is not necessary to assume the sulci to be perpendicular to the slice: for a sulcus with incidence angle b, both h and T in the formula above would acquire identical factors of $\cos(b)$ that cancel out]. Thus, we have $h = T(F_G - 1)$, and

$$2R_w = 2R\left(1 - \frac{TF_G}{R}\right).$$

Thus,

$$A_{W0} = A_E\left(1 - \frac{TF_G}{R}\right)^2.$$

If we now assume a constant GM thickness, then it follows that sulci and anti-sulci must on average be spaced regularly and also have equal depths. This assumption implies that $\Delta A_W = \Delta A_G$. Consider now the expression for F_W:

$$F_W = \frac{A_{W0} + \Delta A_W}{A_E}.$$

By introducing the expressions for A_{W0} and ΔA_W above, we obtain, at last,

$$F_W = F_G + \frac{TF_G}{R}\left[\frac{TF_G}{R} - 2\right].$$

In passing, we note that the requirement that the (nondeformed) GM thickness T be approximately constant may seem too idealized. We do not claim the cortex is shaped like this, even approximately; but our model remains valid for any area- and volume-preserving deformation of this idealized cortex. What the model presupposes therefore is that, on average, real cortices are well approximated by a deformation of an idealized regular cortex with constant thickness along its surface. As we shall see, the model's predictions for the relation between the two folding indexes are remarkably accurate when confronted with empirical data.

Finally, because we claim it is the folding of the WM–GM interface that drives the folding of the cortical surface, it might perhaps seem more sensible to express F_G as a function of F_W and not the other way around. Unfortunately, the resulting expression is not particularly illuminating. Inverting the formula above, we find

$$F_G = \frac{1 + 2\frac{T}{R} + \sqrt{1 + 4\frac{T}{R}\left[1 + \frac{T}{R}(1 - F_W)\right]}}{2\left(\frac{T}{R}\right)^2}.$$

1. Barres BA, Raff MC (1999) Axonal control of oligodendrocyte development. *J Cell Biol* 147:1123–1128.
2. Herculano-Houzel S, Collins CE, Wong P, Kaas JH (2007) Cellular scaling rules for primate brains. *Proc Natl Acad Sci USA* 104:3562–3567.
3. Herculano-Houzel S, Mota B, Lent R (2006) Cellular scaling rules for rodent brains. *Proc Natl Acad Sci USA* 103:12138–12143.

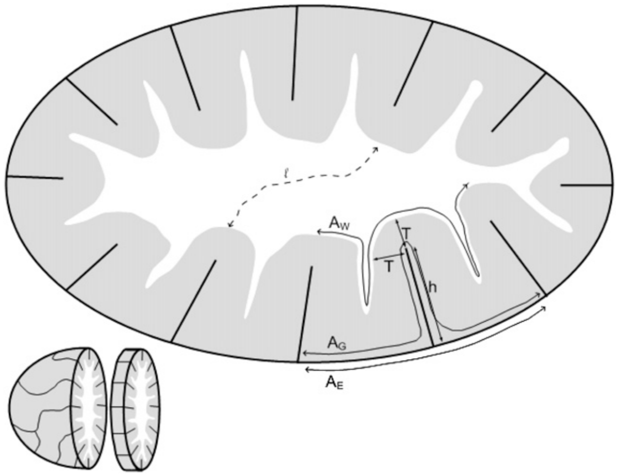

Fig. S1. Schematic representation of a slice of cortex, as indicated in the *inset*, according to this model. Although this is clearly a simplified view of a complex surface, it provides accurate estimates of the various surface area measures, allowing us to relate their respective scaling rules to each other. The total cortical surface area A_G, exposed cortical surface area A_E and WM-GM interface area S_W, as well as the cortical thickness T, average sulci depth h and average *WM* axon length l are indicated.

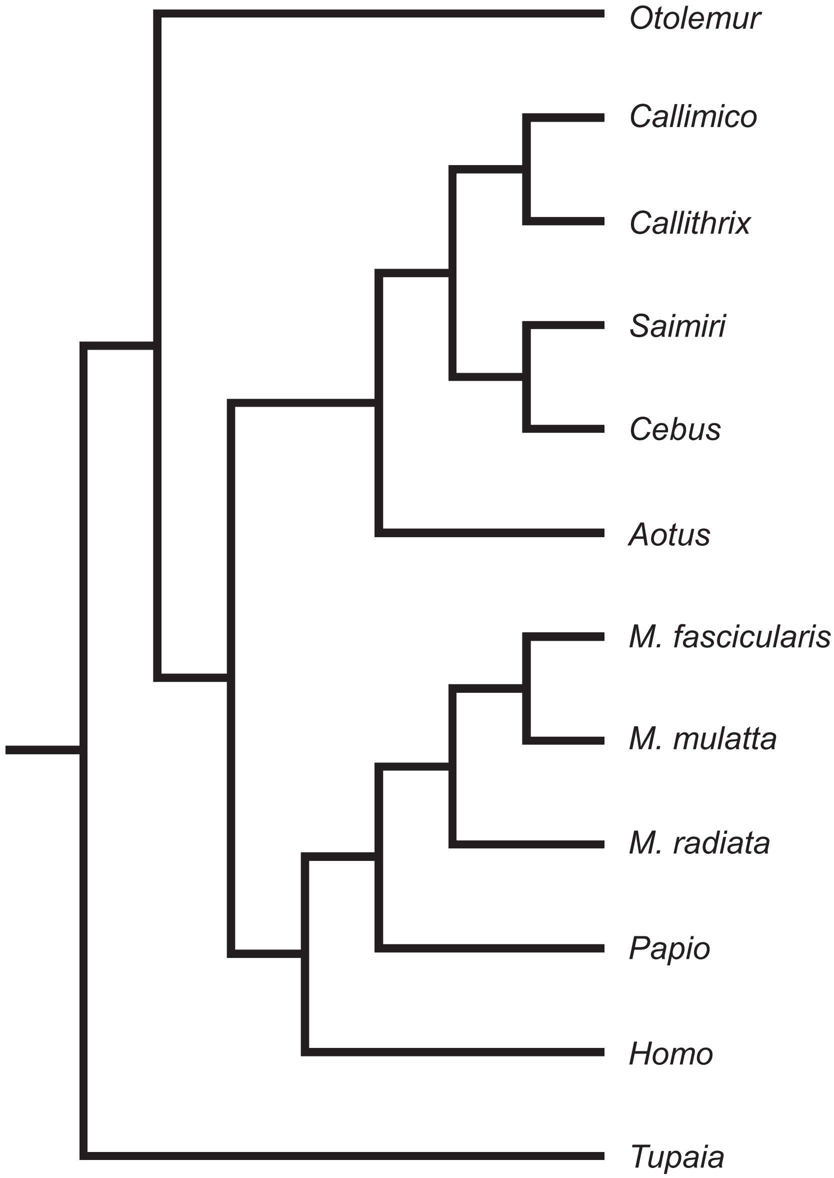

Fig. S2. Phylogenetic relationships among species in the dataset; based on Purvis (1).

1. Purvis A (1995) A composite estimate of primate phylogeny. *Philos Trans R Soc Lond B Biol Sci* 348:405–421.

Table S1. Scaling exponents, raw and corrected for phylogenetic relatedness among species in the dataset

	Contemporary "tip" species data								Independent contrasts		
	Without tree shrew				With tree shrew				All species		
Function	Slope	*P* value	95% CI, lower	95% CI, upper	Slope	*P* value	95% CI, lower	95% CI, upper	Slope	*P* value	r^2
$M_W \sim M_G$	1.153	<0.0001	1.057	1.249	1.148	<0.0001	1.073	1.223	1.149	0.0117	0.972
$V_W \sim V_G$	1.190	<0.0001	1.006	1.374	1.184	<0.0001	1.058	1.310	1.162	<0.0001	0.966
$M_G \sim N$	1.082	<0.0001	0.892	1.273	1.043	<0.0001	0.896	1.190	1.072	0.0010	0.935
$M_{G+W} \sim N$	1.142	<0.0001	0.934	1.350	1.097	<0.0001	0.936	1.258	1.125	0.0117	0.921
$M_W \sim O_W$	1.045	<0.0001	0.944	1.147	1.032	<0.0001	0.952	1.112	1.032	0.0117	0.970
$M_W \sim N$	1.248	<0.0001	1.005	1.491	1.197	<0.0001	1.009	1.385	1.232	0.0117	0.888
$O_W \sim N$	1.199	<0.0001	1.017	1.381	1.165	<0.0001	1.025	1.305	1.193	0.0010	0.950
$A_W \sim V_W$	0.811	<0.0001	0.745	0.876	0.800	<0.0001	0.754	0.847	0.797	<0.0001	0.982
$A_W \sim N$	0.900	<0.0001	0.592	1.208	0.873	<0.0001	0.668	1.078	0.852	<0.0001	0.889
$A_E \sim V_{G+W}$	0.678	<0.0001	0.635	0.721	0.676	<0.0001	0.647	0.706	0.662	<0.0001	0.987
$A_E \sim N$	0.657	<0.0001	0.409	0.905	0.652	<0.0001	0.488	0.816	0.641	0.0002	0.845
$F_W \sim N$	0.243	<0.0001	0.170	0.316	0.220	<0.0001	0.168	0.273	0.222	<0.0001	0.926

Slopes refer to least-squares regression of the raw data to power functions ("contemporary tip species data") or to reduced major axis regression of log-transformed data to linear functions (independent contrasts), using the PDAP module of the Mesquite software package. All datasets include data for the human brain. A_E, exposed surface area of cerebral cortex; A_W,WM–GM interface surface area; CI, confidence interval; F_W, WM folding index; M_G, mass of cerebral cortex GM; M_{G+W}, total mass of cerebral cortex; M_W, mass of cerebral cortex WM; *N*, number of neurons in the cerebral cortex; O_W, number of other (nonneuronal) cells in WM; V_G, volume of GM; V_W, volume of WM; V_{G+W}, total volume of cerebral cortex.

Table S2. Average mass and cellular composition of the subcortical white matter

Species	M_{G+W}	M_G	M_W	% M_W	N_{G+W}	O_W	F_G
Tupaia glis (*n* = 2)	0.705	0.515 ± 0.063	0.190	26.95	21.95 ± 1.60	16.22	1.04
Callithrix jacchus (*n* = 3)	2.842	2.042 ± 0.120	0.800	28.15	120.33 ± 43.30	74.63	1.18
Otolemur garnetii (*n* = 2)	3.396	2.556 ± 0.129	0.840	24.74	88.50 ± 14.75	102.89	1.25
Aotus trivirgatus (*n* = 3)	5.568	3.698 ± 0.663	1.870	33.58	200.32 ± 67.34	170.04	1.36
Callimico goeldii (*n* = 1)	6.492	3.872	2.620	40.36	178.77	157.13	1.26
Saimiri sciureus (*n* = 3)	10.646	6.996 ± 0.356	3.650	34.28	645.73 ± 43.74	353.05	1.57
Macaca fascicularis (*n* = 1)	18.109	10.459	7.650	42.24	400.74	484.40	1.65
Macaca radiata (*n* = 1)	24.133	15.493	8.640	35.80	829.60	841.38	1.81
Cebus apella (*n* = 2)	24.180	15.820 ± 4.982	8.360	34.57	930.67 ± 507.78	868.73	1.69
Macaca mulatta (*n* = 1)	34.530	21.430	13.100	37.94	795.52	945.94	
Papio cynocephalus (*n* = 2)	59.214	36.334 ± 8.233	22.880	36.84	1,420.34 ± 18.07	1,860.00	1.92
Homo sapiens (*n* = 4)	547.180	285.860	261.320	47.76	7,530	18,480.00	

All values are average ± SD and refer to one cerebral cortical hemisphere only. M_{G+W}, mass of the combined GM and WM of the cerebral cortex (grams); M_G, GM mass (grams); M_W, WM mass (grams); % M_W, relative mass of the WM compared with M_{G+W}; N_{G+W}, number of neurons in the GM and WM (in millions); O_W, number of other (nonneuronal) cells in the WM (in millions); F_G, folding index of the GM (total GM surface/exposed GM surface).