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Principles underlying mammalian neocortical scaling

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Abstract. The neocortex undergoes a complex transformation from mouse to whale. Whereas synapse density remains the same, neuron density decreases as a function of gray matter volume to the power of around $-1/3$, total convoluted surface area increases as a function of gray matter volume to the power of around $8/9$, and white matter volume disproportionately increases as a function of gray matter volume to the power of around $4/3$. These phylogenetic scaling relationships (including others such as neuron number, neocortex thickness, soma radius, and number of cortical areas) are clues to understanding the principles driving neocortex organization, but there is currently no theory that can explain why these neocortical quantities scale as they do. Here I present a two-part model that explains these neocortical allometric scaling laws. The first part of the model is a special case of the physico-mathematical model recently put forward to explain the quarter power scaling laws in biology. It states that the neocortex is a space-filling neural network through which materials are efficiently transported, and that synapse sizes do not vary as a function of gray matter volume. The second part of the model states that the neocortex is economically organized into functionally specialized areas whose extent of area-interconnectedness does not vary as a function of gray matter volume. The model predicts, among other things, that the number of areas and the soma radius increase as a function of gray matter volume to the power of $1/3$ and $1/9$, respectively, and empirical support is demonstrated for each. Also, the scaling relationships imply that, although the percentage of the total number of neurons to which a neuron connects falls as a function of gray matter volume with exponent $-1/3$, the network diameter of the neocortex is invariant at around two. Finally, I discuss how a similar approach may have promise in explaining the scaling relationships for the brain and other organs as a function of body mass.

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1 Introduction

Large airplanes are not simply bigger versions of small airplanes; while a large plane has longer wings, its pilot seat is essentially no different in size than that of a small plane. There is a good reason for this: planes are for flying and thus the wing length must increase as a function of the plane's mass in order to get sufficient lift, but planes are piloted by people who are the same size no matter whether piloting a small or large plane, and thus the pilot seat size must stay the same. The way that wing length and pilot seat size scale with plane weight, then, helps to indicate why planes are built the way they are. An analogous point can be made about mammalian neocortex: whale neocortex is not simply a bigger version of mouse neocortex. Whereas the neocortex of a whale has more neurons, greater thickness, greater surface area, and more white matter than that of a mouse, whale neocortex has lower neuron density and the same synapse density. Furthermore, of those neocortical quantities just mentioned that increase with neocortical gray matter volume, none increase in proportion to gray matter volume. Just as wing length and pilot seat size scaling can help one understand principles underlying why planes are built the way they are, how these neocortical quantities scale may indicate principles underlying why the neocortex is built the way it is.

Neocortical quantities Y have been found to change as a function of neocortical gray matter volume V_{gray} with allometric scaling laws of the form $Y = Y_0 V_{\text{gray}}^b$, where b is the scaling exponent and Y_0 is a constant characteristic of the kind of mammal (it is said that Y is *invariant* with respect to V_{gray} if $b = 0$). Scaling exponents in biology are often simple fractions resulting from underlying mathematical and physical principles, such as the exponent $2/3$ for the scaling of organism surface area

against volume and the exponent 3/4 for the scaling of organism metabolism against body mass (Schmidt-Nielson 1984). Measurements of scaling exponents for neocortical quantities go back at least to Tower (1954), who measured a neuron density scaling exponent of around $-1/3$. Since then many other scaling exponents have been measured; for example, synapse density has been found to be invariant, neocortical thickness (from pia to white matter) has been measured to be around 1/9, neocortical total convoluted surface area has been measured to be around 8/9, and white matter volume has been measured to be around 4/3 (see Table 1 for references). No prior theory explains these scaling laws satisfactorily. My model explains these exponents, and consists of two parts. The first part of the model emanates from a recent physico-mathematical model of West et al. (1997) that is used to explain, among other things, the 3/4 scaling exponent for metabolic rates of organisms as a function of body mass. Their model concerns the efficient distribution of materials through space-filling branching networks whose terminal segments are not a function of body size. Their hypothesis can be applied to neural networks, and is a key part in the explanation of the neocortical scaling exponents. The second part of the model concerns the large-scale organization of the neocortex, claiming that it is composed of functionally specialized areas whose extent of area interconnectedness (to be defined later) is invariant, and whose connection costs are minimized.

2 Synapse density

Nearly all explanations for neocortex scaling laws depend on the fact that synapse density is independent of brain size (Abeles 1991). Little attention has been given to explaining this invariance, however, perhaps because investigators are typically more interested in trends than non-trends. Synapse density invariance is explained by the model mentioned above from West et al. (1997). The model is recorded in more detail here as Model 1, which has three assumptions, or principles.

Table 1. Predicted and measured scaling exponents for neocortical variables against gray matter volume V_{gray}. The measured exponents are in most cases acquired from scaling data against brain volume. To obtain exponents against V_{gray}, I have assumed that V_{gray} is proportional to brain volume. This proportionality is empirically justified, as measured exponents for V_{gray} to brain volume are close to one: 0.983 (Prothero 1997a), 0.982 (Hofman 1991), 1.054 (Hofman 1989), 1.04 (Prothero and Sundsten 1984), 1.06 (Frahm et al. 1982), and 1.08 (Jerison 1982). "i.d." means that there are insufficient data to compute a scaling exponent, although the prediction is broadly consistent with the data

Variable description	Variable	Predicted exponent	Measured exponent	References
Synapse density	ρ_{synapse}	$0 = 0.00$	0	Abeles 1991
Neuron number	N	$2/3 = 0.67$	0.62	Jerison 1973
			0.67	Passingham 1973
Neuron density	ρ_{neuron}	$-1/3 = -0.33$	−0.312	Prothero 1997b
			−0.28	Prothero 1997b
			−0.28	Tower 1954
			−0.32	Tower 1954
Number of synapses per neuron	s	$1/3 = 0.33$	i.d.	
Number of areas	A	$1/3 = 0.33$	0.40	This paper (see Fig. 3)
Thickness	T	$1/9 = 0.11$	0.092	Prothero 1997a
			0.115	Prothero 1997a
			0.129	Hofman 1991
			0.197	Hofman 1989
			0.08	Prothero and Sundsten 1984
			0.17	Jerison 1982
Total surface area	S	$8/9 = 0.89$	0.905	Prothero 1997a
			0.893	Prothero 1997a
			0.922	Prothero 1997a
			0.901	Hofman 1991
			0.899	Hofman 1989
			0.89	Hofman 1985
			0.91	Prothero and Sundsten 1984
			0.91	Jerison 1982
Soma radius	R_0	$1/9 = 0.11$	0.10	This paper (see Fig. 4)
Axon radius	R_1	$1/9 = 0.11$	i.d.	
Volume of white matter	V_{white}	$4/3 = 1.33$	1.318	Allman 1999
			0.985	Prothero 1997b
			1.28	Hofman 1991
			1.37	Hofman 1989
			1.31	Frahm et al. 1982

Assumption 1.1 states that the neocortical neural network has space-filling branching patterns, each neuron filling its own portion of the gray matter. That neurons are space-filling has empirical support (Porter et al. 1991; Panico and Sterling 1995), and the reason the neocortical neural network is space-filling is presumably in order to minimize the total volume required for the network. Assumption 1.2 says that synapse size (e.g., terminal bouton diameter) is invariant. It is empirically supported because while synapses do vary in size within the neocortex, they do not vary in size as a function of V_{gray} (Abeles 1991). Assumption 1.3 is that neuron arbor diameters follow Murray's Law (Murray 1926), which states that the cube of the parent segment's diameter is equal to the sum of the cubes of each daughter segment's diameter. Neuron arbor diameters for many varieties of neurons including pyramidal cells have been shown to fit Murray's Law (Cherniak et al. 1999). One explanation for why Murray's Law applies to neuron arbors is that neuron arbor diameters are set in such a way as to minimize the power required to distribute materials via laminar fluid flow throughout the network (Cherniak et al. 1999). In fact, it is well known that there is fluid flow in neural arbors (Lasek 1988), and that the fluid flow is laminar follows from the facts that fluid flow in pipes of diameter less than one millimeter tends to be laminar (Streeter and Wylie 1985), and that neural arbors have diameters on the micron scale. West et al. (1997, p. 124) show that in a tree satisfying Model 1 the number of leaves is proportional to the body volume. ''Number of leaves'' becomes, for our network, ''number of synapses per neuron.'' ''Body volume'' becomes ''volume of cortex filled by the neuron.'' Thus, the number of synapses per neuron is proportional to the volume of the cortex filled by the neuron. Since synapse density is proportional to the number of synapses per neuron divided by the volume of gray matter the neuron fills (because of Assumption 1.1), synapse density is invariant.

3 Neuron number and density

Neocortical neuron density has been found to have an exponent around -0.3, and neuron number N an exponent around 0.65 (see Table 1). The speculation since Tower (1954) has been that the exponents are, respectively, $-1/3$ and $2/3$. Because about 85% of neocortical neurons are pyramidal cells (Schüz 1998), and only pyramidal cells significantly change in their degree of arborization from mouse to whale (Deacon 1990), it is changes to pyramidal cells that must account for the decreasing neuron density. Accordingly, neuron number and density will refer to pyramidal neurons. Also, because most (over 90%) of the neocortical connections are from one part of neocortex to another (Braitenberg 1978), the other neocortical connections are probably not the principal drivers of neocortical scaling; I will therefore concentrate on the cortico-cortical connections only.

What explains the neuron density scaling exponent of $-1/3$? The only attempt at a quantitative explanation of the neuron density scaling exponent has been Prothero's repeating units model (Prothero 1997a). His model possesses, however, the assumption that the number of ''repeating units'' – a hypothetical piece of neocortex spanning the thickness of neocortex and having a fixed number of neurons, possibly much like a minicolumn or radial unit (Rakic 1995) – is proportional to the visible outer surface area of the brain (as opposed to the total, convoluted surface area). Because the outer, visible surface area scales as the 2/3 power of brain volume, and the number of neurons per unit is invariant, it easily follows that neuron number scales against brain volume with an exponent of 2/3. This is unsatisfying, however, because why repeating units should scale in proportion to the outer surface area rather than the total convoluted surface area is just as mysterious, and is in need of just as much explanation as why neuron number should scale with brain volume to the 2/3 power.

My model's second part, Model 2, explains the neuron density scaling law, and is comprised of four assumptions, or principles. The neocortex is parcelled into functionally specialized areas (Kaas 1987; Northcutt and Kaas 1995). My model defines areas as groups of neurons for which inter-area connections are made using pyramidal neurons via the white matter, and intra-area connections are made locally. Assumption 2.1 states that a single pyramidal neuron's axon can innervate only one area. An area connects to a certain percentage of the other areas. This percentage is the *percent area-interconnectedness*. Assumption 2.2 states that the average percent area-interconnectedness remains roughly constant whatever the total number of areas. The motivation for this is that each area has its own specialized task it carries out, and in order for an area's efforts to be useful it must make its results known to an invariant percentage of the areas in the neocortex (see Fig. 1). Areas are composed of many neurons, and thus a connection from one area to another is always from a neuron in the first area to a certain percentage of the neurons in the second area. This percentage is the *percent area-infiltration*. Assumption 2.3 states that whatever the neocortical gray matter volume, the average percent area-infiltration stays roughly the same. The motivation for this is that when an area tells another area about its efforts, it must tell a certain invariant percentage of the neurons in the area in order for the area to understand and appropriately respond to the news (see Fig. 2). All things being equal, it is advantageous for a central nervous system to use less neural wiring, and certain aspects of neuroanatomy and structural organization have been found to be consistent with wire-optimization hypotheses (Durbin and Mitchison 1990; Mitchison 1991, 1992; Jacobs and Jordan 1992; Cherniak 1992, 1994, 1995; Ruppin et al. 1993; Van Essen 1997; Cherniak et al. 1999). Under a save-wire desideratum we would expect that the neocortex would satisfy Assumptions 2.1, 2.2, and 2.3 in a fashion sensitive to the connection costs. In particular, we would expect that the average number of neurons to which a neuron's axon connects – the *average neuron degree*, δ – will not be much greater than that needed to satisfy these other hypotheses. Why? Because connecting to more neurons requires a greater number of synapses per

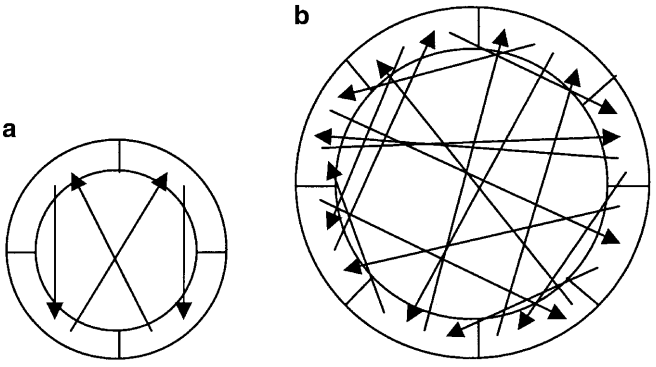

Fig. 1a,b. The invariance of percent area-interconnectedness. The average percent area-interconnectedness in a small and large neocortex; Assumption 2.2 states that it is invariant. The *outer part* of each *ring* depicts the gray matter, the *inner part* the white matter. Each neocortex has multiple areas. **a** Each of the four areas in this small neocortex connects to one other area. The average percent area-interconnectedness is thus 1/4. **b** Each of the eight areas in this large neocortex connects to two other areas. The average percent area-interconnectedness is thus 2/8 = 1/4, the same as for the small brain

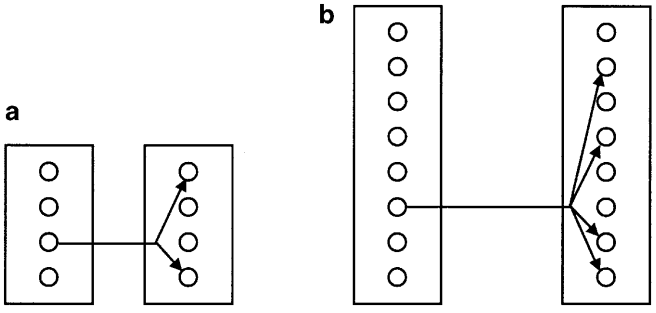

Fig. 2a,b. The invariance of percent area-infiltration. The average percent area-infiltration for small and large areas; Assumption 2.3 states that it is invariant. Each *rectangle* depicts an area, and each *small circle* a pyramidal neuron. **a** Each of these two areas has four neurons, and the *left area* connects via a pyramidal axon to two neurons in the *right area*. The percent area-infiltration is 2/4 = 1/2. The other neurons' connections are not shown. **b** Each of the two areas has eight neurons, and the *left area* connects to four neurons in the *right area*. The percent area-infiltration is 4/8 = 1/2, the same as for the small area

neuron, and this, in turn, requires greater arborization – more wire. In terms of scaling, this save-wire expectation can be weakened to the expectation that the average neuron degree scales no faster than needed to satisfy the first three hypotheses; this comprises Assumption 2.4. Informally, Model 2 says that no matter the neocortex size, an area talks to a fixed fraction of all the areas, and when an area talks to another area it informs a fixed fraction of the neurons in that area; furthermore, this is done in an efficient manner. Note that, unlike in Model 1 where there is independent evidence supporting each hypothesis, there does not yet exist independent support for the hypotheses in Model 2 (especially Assumptions 2.2 and 2.3); these hypotheses are assumptions of the model. Also, it should be recognized that from these assumptions we cannot make predictions concerning the large-scale organization of any particular neocortex; these assumptions are "zeroth-order" approximations, and only touch on how neocortical quantities change, across animals, as a function of V_{gray}.

From Model 2 we may derive the neuron density and other scaling exponents. Some notation is required: let A be the total number of areas, D be the average number of areas to which each area connects, and W be the average number of neurons per area; also recall that δ is the average neuron degree (i.e., the average number of neurons to which a neuron's axon connects). D/A is the average percent area-interconnectedness, and by Assumption 2.2 it is invariant, so $D \sim A$. δ/W is the average percent area-infiltration, and by Assumption 2.3 it is also invariant, so $\delta \sim W$. There must be sufficiently many neurons in an area to connect to D areas, so it must be that $W \geq D$ (via Assumption 2.1). Because $\delta \sim W$ and because Assumption 2.4 says that δ scales no faster than necessary, W must scale no faster than necessary, thus $W \sim D$. Putting things together, we now have $\delta \sim W \sim D \sim A$. Since the total number of neurons $N \sim AW$, it follows that $\delta \sim W \sim D \sim A \sim N^{1/2}$. Schüz (1998) argues that, to a good approximation, a pyramidal neuron connects to almost as many different neurons as its number of axon synapses (an "axon synapse" is a presynaptic terminal from an axonal arbor), which strongly suggests the much weaker proposition that δ is proportional to the average number of axon synapses per neuron, s. Although there is no measured scaling exponent for s, it can be computed using the neuron density exponent as follows (where ρ_{synapse} and ρ_{neuron} are the neocortical synapse and neuron densities, respectively): $s = \rho_{\text{synapse}}/\rho_{\text{neuron}}$. Thus, $\delta \sim \rho_{\text{synapse}}/\rho_{\text{neuron}}$, and since ρ_{synapse} is invariant, $\delta \sim 1/\rho_{\text{neuron}}$. Also, ρ_{neuron} is defined as N/V_{gray}, so $\delta \sim V_{\text{gray}}/N$. Since we have seen just above that $\delta \sim N^{1/2}$, it follows that $V_{\text{gray}}/N \sim N^{1/2}$. Solving for N we have $N \sim V_{\text{gray}}^{2/3}$. Dividing each side by V_{gray}, we have $\rho_{\text{neuron}} \sim V_{\text{gray}}^{-1/3}$.

Note that it also follows that the total number of areas scales as gray matter volume to the power of 1/3; i.e., $A \sim V_{\text{gray}}^{1/3}$. This is consistent with currently available data, as can be seen in Fig. 3. This suggests that the number of areas increases in neocortex not because of a selective pressure for greater modularity and specialization, but because of the requirement that the neocortex arrange itself so as to economically achieve an invariant degree of well-connectedness. While my model explains the quantitative increase in the number of cortical areas, it does not explain why there are areas in the first place; that is, my model presumes there *are* areas. It has been argued that the fact that there are areas at all may, itself, be due to a pressure to optimize volume (Durbin and Mitchison 1990; Mitchison 1991, 1992; Ringo 1991; Jacobs and Jordan 1992; Ringo et al. 1994).

4 Surface area, thickness, axon diameter, soma diameter, and white matter volume

Neocortical total surface area and thickness scaling exponents were computed first by Jerison (1982), and have since been measured by others (see Table 1). The

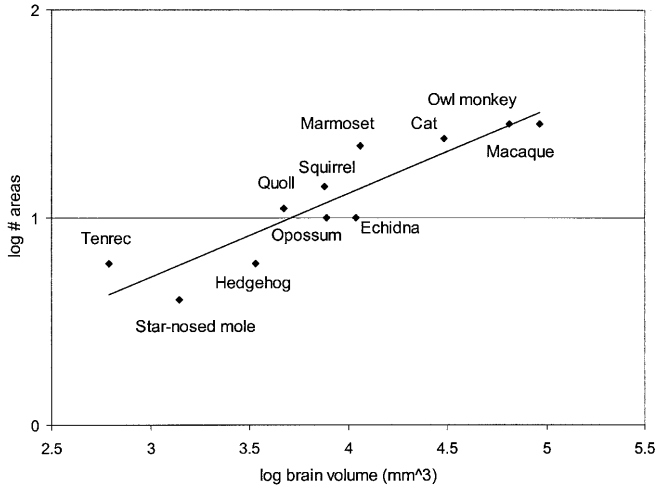

Fig. 3. Logarithm (base 10) of the number of cortical areas versus logarithm of brain volume. Best-fit line via linear regression is $y = 0.4032x - 0.4988$ ($R^2 = 0.8197$, $n = 11$, $p < 0.001$), the slope of which is not significantly different from 1/3 ($p > 0.2$). Counts of cortical areas taken from Kaas (1987), Krubitzer (1995), and Krubitzer et al. (1997). There are disagreements on how to distinguish and count areas, but while different methodologies are likely to lead to different constants in the scaling law, they are unlikely to lead to different scaling exponents. By confining area counts to within a single methodology (i.e., that of Kaas and colleagues), we expect a reasonable estimate of the exponent. Brain volumes are taken from Frahm et al. (1982), Haug (1987), Hofman (1982a,b, 1983, 1985), Hrdlicka (1907), and Stephan et al. (1981). The x-axis is brain volume, but since it scales proportionally to gray matter volume (see caption of Table 1), the slope of the line in the plot gives the best-fit exponent for the number of areas as a function of gray matter volume. Log-log (x, y) values plotted are: star-nosed mole (3.15, 0.60), hedgehog (3.53, 0.78), tenrec (2.79, 0.78), echidna (4.04, 1.00), opossum (3.89, 1.00), quoll (3.67, 1.04), squirrel (3.88, 1.15), marmoset (4.60, 1.34), cat (4.49, 1.38), owl monkey (4.81, 1.45), and macaque (4.97, 1.45). Note that if we add a point for human, somewhat arbitrarily using 50 as the number of areas (log-log point = (6.13, 1.70)), the slope becomes 0.34 ($R^2 = 0.8429$)

scaling exponent for surface area S has hovered around 0.9, and that for thickness T around 0.1. Rockel et al. (1980) have shown that the number of neurons along a thin line through the thickness of the cortex is invariant. Assuming that the neuron density decrease is isotropic, the line density decrease along a line through the thickness of the cortex will scale at $(-1/3)/3 = -1/9$ (Prothero 1997b). Since the number of neurons along this line is invariant, $T \sim V_{\text{gray}}^{1/9}$. Also, $ST = V_{\text{gray}}$, and so $S \sim V_{\text{gray}}^{8/9}$. These are in close agreement with the measured exponents shown in Table 1.

There has been some confusion concerning how the results of Rockel et al. (1980) should be considered in light of the, at first glance, contradictory conclusion by Haug (1987) that the number of cortical neurons beneath a square millimeter of cortical surface decreases in larger gray matter volumes. Prothero (1997b) examines and resolves this seeming paradox: the counts of Rockel et al. (1980) are of the number of neurons along a thin line through cortex (although from this they invalidly extrapolate an invariant neuron density), whereas Haug's values (Haug 1987, Fig. 13) are of the number of neurons under a square millimeter of cortex. The former is a measure of the number of neurons from pia to white matter and is unaffected by the decreasing neuron density, whereas the latter is affected by the decreasing neuron density. In short, the results of Rockel et al. (1980) and Haug (1987) tell us distinct, compatible things.

A scaling exponent for white matter volume was computed first by Frahm et al. (1982), and has since been measured by other investigators (see Table 1). Almost all the scaling exponents are around 1.3, and one conjecture has been that the exponent is 4/3 (Allman 1999). White matter volume, then, scales disproportionately fast compared to V_{gray}.

White matter consists of myelinated pyramidal axons, and one might expect that white matter volume scaling depends in part on how axon radius scales. Axon radius R_1 can be derived from the model as follows. West et al. (1997) show that a tree satisfying Model 1 possesses a first segment, or trunk, whose radius scales in proportion to the number of leaves on the tree to the power of 1/3. We may treat each white matter axon as the trunk of the axonal tree that reaches back into the gray matter. Thus, axon radius R_1 scales as the average number of axon synapses per neuron, s, to the power of 1/3; i.e., $R_1 \sim s^{1/3}$. We saw earlier that $s = \rho_{\text{synapse}}/\rho_{\text{neuron}}$, and so $s \sim V_{\text{gray}}^{1/3}$ (this utilized Model 2). Therefore, the model predicts that $R_1 \sim V_{\text{gray}}^{1/9}$. Under the model being proposed, then, axon radius increases with increasing gray matter volume not because of transmission time considerations, but because of the need to efficiently distribute materials via a laminar fluid through a space-filling branching network whose terminal segments are not a function of body size, i.e., because of the physico-mathematical Model 1. However shorter transmission times will be a fortunate consequence of increased axon radius (Rushton 1951).

Is there any evidence to confirm the prediction that $R_1 \sim V_{\text{gray}}^{1/9}$? First, note that the prediction that axon radius increases as the number of axon synapses per neuron increases (but less quickly) should not be at all surprising: in natural tree structures (e.g., arteries, veins, plants, river drainage networks, and river deltas), if a segment supports a greater number of leaves, then, all things being equal, the segment has greater radius. This is no less true of neurons (Cherniak et al. 1999). Thus, if we are confident that the number of axon synapses per neuron increases as a function of gray matter volume (i.e., if we are confident that synapse density is invariant but neuron density decreases), then we must also be confident that axon radius increases as a function of gray matter volume. There currently are, however, insufficient data to test this directly. The only comparitive data on pyramidal axon radius of which I am aware are from Jerison (see Schüz and Preiß1 1996, Fig. 3) for just two animals (mouse and monkey): the frequency distributions for myelinated fiber cross-sectional area in each animal overlap a great deal, but about 20% of the fibers in monkey form an extended tail in the distribution into fiber cross-sectional areas up to around two to three times the maximum found in mouse. There is an indirect way of testing the prediction if axon radius can be assumed to scale in proportion to the soma radius R_0. In fact, a

consequence of Model 1 is that a parent segment radius scales in proportion to any of its immediate daughter segment radii (West et al. 1997); so, if the soma can be treated as the parent segment of the myelinated white matter axon, we would expect soma radius to scale proportionally with axon radius. Haug (1987, Fig. 8) finds a small but significant ($p = 0.05$) correlation between soma size for cortical neurons and brain volume (but insignificant correlation when confined to just to primates); no scaling exponent is given and the data presentation is not susceptible to my own attempts to compute it. A scaling exponent for soma radius versus gray matter volume can be computed using data from Purves (1988): the soma radius scaling exponent was computed to be 0.10 (see Fig. 4), in close agreement to the predicted 1/9. However, these data are for spinal motor neurons, not cortical neurons (see the legend of Fig. 4).

The white matter volume scaling exponent is derived as follows. White matter volume, V_{white}, is proportional to the number of white matter axons, $N_{\text{whiteaxon}}$, times the volume of a white matter axon, $V_{\text{whiteaxon}}$; i.e., $V_{\text{white}} \sim N_{\text{whiteaxon}} V_{\text{whiteaxon}}$. Consider $N_{\text{whiteaxon}}$, first. $N_{\text{whiteaxon}}$, is proportional to the number of areas, A, times the average number of areas to which each area connects, D; i.e., $N_{\text{whiteaxon}} \sim AD$. In the derivation of the neuron density exponent we had shown that $A \sim D \sim N^{1/2}$. Since $N \sim V_{\text{gray}}^{2/3}$, it follows that $A \sim D \sim V_{\text{gray}}^{1/3}$. Therefore, $N_{\text{whiteaxon}} \sim V_{\text{gray}}^{2/3}$. Now consider the volume of a white matter axon, $V_{\text{whiteaxon}}$. $V_{\text{whiteaxon}}$ is proportional to the length of a white matter axon, L, times the square of its radius, R_1; i.e., $V_{\text{whiteaxon}} \sim L R_1^2 \; R_1 \sim V_{\text{gray}}^{1/9}$ from above. Since white matter axons must travel a distance proportional to the diameter of the white matter volume, and because white matter appears to enlarge proportionally in all three dimensions, $L \sim V_{\text{white}}^{1/3}$. Therefore, $V_{\text{whiteaxon}} \sim V_{\text{white}}^{1/3} V_{\text{gray}}^{2/9}$. Putting these scaling relations together we get that $V_{\text{white}} \sim N_{\text{whiteaxon}} V_{\text{whiteaxon}} \sim V_{\text{gray}}^{2/3} V_{\text{white}}^{1/3} V_{\text{gray}}^{2/9}$. Solving for V_{white}, we have $V_{\text{white}} \sim V_{\text{gray}}^{4/3}$, in close agreement with most of the measured exponents (Table 1).

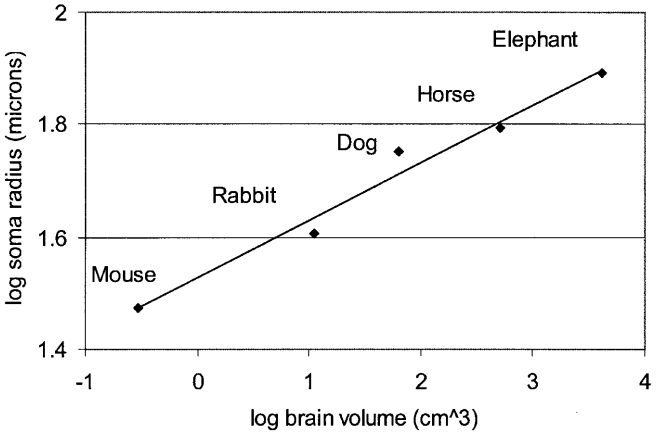

Fig. 4. Logarithm of soma radius versus logarithm of brain volume. Best-fit line via linear regression is $y = 0.102x + 1.527$ ($R^2 = 0.9773$, $n = 5$, $p < 0.001$), which has a slope very near the predicted exponent of 1/9. Soma radii taken from Purves (1988, p. 65) and brain volumes from Haug (1987, p. 128). Soma radii are from spinal motor neurons, and are directly relevant to pyramidal neurons under the assumption that each kind of neurons scales similarly (e.g., that, for each neuron kind, the number of synapses per neuron scales the same, from which we can derive (see main text) identical scaling for soma radius). Log-log (x, y) values plotted are: mouse (−0.52, 1.47), rabbit (1.05, 1.61), dog (1.80, 1.75), horse (2.71, 1.79), and elephant (3.62, 1.89)

Note that if axon radius were invariant, the volume of a white matter axon would be proportional to the white matter volume to the power of 1/3. The resulting proportionality equation would instead be $V_{\text{white}} \sim N_{\text{white}} V_{\text{whiteaxon}} \sim V_{\text{gray}}^{2/3} V_{\text{white}}^{1/3}$, and the resulting scaling exponent for the volume of white matter against gray matter volume would then be one. Therefore, the reason white matter volume scales disproportionately quickly compared to gray matter volume is not because of a disproportionate increase in the number of white matter axons, but, instead, because of the increasing axon radius due to the physico-mathematical constraints on the network.

5 Neuron interconnectedness and network diameter

Using these scaling relationships we may examine the consequences of how neuron interconnectedness scales. One way to measure neuron interconnectedness is via the *average percent neuron-interconnectedness* of neurons, where a given *percent neuron-interconnectedness* of a neuron is the percentage of all neurons to which it connects; i.e., average percent neuron-interconnectedness is equal to δ/N, where N is the total number of neurons and δ is the average neuron degree (i.e., the average number of neurons to which a neuron's axon connects). To calculate how the average percent neuron-interconnectedness scales it is necessary to estimate the scaling exponent for the average neuron degree δ. Recall from Sec. 3 that $\delta \sim 1/\rho_{\text{neuron}}$. Since $\rho_{\text{neuron}} \sim V_{\text{gray}}^{-1/3}$, it follows that $\delta \sim V_{\text{gray}}^{1/3}$, which is consistent with the trend that a larger neocortex has a greater number of synapses per neuron (Abeles 1991). Since $N \sim V_{\text{gray}}^{2/3}$, the average percent neuron-interconnectedness is, then, $\delta/N \sim N_{\text{gray}}^{-1/3}$. Thus, the average percent neuron-interconnectedness decreases with increasing gray matter volume, and some authors have pointed out that this is to be expected, as maintenance of a constant average percent neuron-interconnectedness would be unfeasible (Stevens 1989; Deacon 1990; Ringo 1991).

Average percent neuron-interconnectedness is an overly strong notion of neural interconnectedness, however. A more appropriate measure might be the *network diameter*, which is defined as – over all pairs of neurons – the average number of "edges" (i.e., axons) along the shortest path connecting the pair. Intuitively, network diameter measures how close – in terms of connectivity – neurons are to one another, on average. Despite the decreasing average percent neuron-interconnectedness, it is quite possible that the network diameter remains constant and low as V_{gray} increases, as we will now see. In a random network the network diameter is approximately $(\log N)/(\log \delta)$ (Bollobás 1985, p. 233). The neocortex is certainly not a random net-

work, but because pyramidal neurons usually make long-range connections (or "shortcuts") via the white matter, the network may be a *small world network* (Watts and Strogatz 1998) which is non-random yet has a network diameter nearly as low as that for a random network. Because $N \sim N_{\text{gray}}^{2/3}$ and $\delta \sim V_{\text{gray}}^{1/3}$, $N \sim \delta^2$. The network diameter would, then, be approximately $[\log (C\delta^2)]/[\log \delta] = 2 + (\log C)/(\log \delta)$, where C is a proportionality constant. That is, for sufficiently large V_{gray}, the neuron degree δ becomes large and thus the network diameter approaches two; in the limit there are on average only two edges – one neuron – separating any pair of neurons. A rough estimate of the constant C can be obtained by comparing actual values of neuron number N and the average neuron degree δ. For a mouse, $N \approx 2 \times 10^7$ and $\delta \approx 8000$ (Schüz 1998), so the constant $C \approx N/\delta^2 = 0.3$. Common estimates for human are around $N \approx 10^{10}$ and $\delta \approx 50\,000$ (Abeles 1991), making the constant $C \approx 4$. What is important here is that these estimates of C: (i) are of order one, and (ii) are well below the estimates of δ. Thus $(\log C)/(\log \delta) \approx 0$ and the network diameter is approximately two. As a point of comparison, note that the network diameter for *Caenorhabditis Elegans* – the only nervous system for which the network diameter has been explicitly measured – is 2.65 (Watts and Strogatz 1998); its network diameter computed via the random network approximation is 2.16. This suggests the conjecture that a network diameter around two is a feature common to all central nervous systems.

6 Conclusion and discussion

The way that neocortical quantities scale as gray matter volume V_{gray} increases suggests that the neocortex consists of anatomically distinct areas: (i) that must connect, on average, to a certain percentage of the total number of areas no matter how many areas there are; and (ii) whose area-to-area connections must connect, on average, to a certain percentage of the neurons in an area no matter how many neurons are in the area. Furthermore, all this is satisfied in a way sensitive to the pressure to optimize volume. The physico-mathematical Model 1 concerned the efficient distribution of materials through a space-filling, leaf-size-invariant network, and was an essential piece in the explanation of the scaling exponents. This highlights an under-recognized and under-utilized explanatory avenue in neuroscience, that of explaining phenomena by recourse, in part, to the underlying physical and mathematical constraints.

It may be that such constraints, which have recently been useful in explaining metabolic scaling, also explain why brain mass scales as body mass M to the power of 3/4 (see, e.g., Allman 1999). Consider the following preliminary qualitative argument. Under the assumptions that: (a) metabolic rate is proportional to blood flow, and (b) capillary diffusing-ability is invariant and so blood flow is proportional to the total number of capillaries N_{cap}, it follows that $N_{\text{cap}} \sim M^{3/4}$ (West et al. 1997). If organ A has greater capillary density than organ B, then we expect organ A's scaling behavior to be driven more by the scaling behavior of capillaries than is organ B's. Intuitively, organ A will have to enlarge less quickly in larger animals than organ B because, as each organ enlarges, the "capillary portion" of each does not have to enlarge as quickly as the "non-capillary portion" of each, and organ A has a greater percentage of "capillary portion" than organ B. One measure of the capillary density of an organ is the metabolic rate per gram of the organ (Ross et al. 1989, p. 311), and there exist data for the latter. The prediction of this argument is that organs with greater metabolic rates per gram should have lower scaling exponents against body mass. To test this prediction, I compiled metabolic rates per gram for organs in mouse, rat, and dog, and normalized them; also, for each organ I obtained from the literature the scaling exponent. These values can be found in Table 2.

Table 2. Metabolic rates per gram are shown for various organs in mouse (Martin and Fuhrman 1955), rat (Field et al. 1939), and dog (Martin and Fuhrman 1955). Because larger animals have lower metabolisms, we cannot simply average across the three animals. Instead, for each animal the values are normalized in the interval [0, 1], and then the average and standard deviation (SD) are computed. The scaling exponent for M_{organ} as a function of body mass M is shown, along with the citation for the exponent. The exponents are plotted against the average normalized metabolic values in Fig. 5

Organ	Metabolic rate per gram (ml O_2/(g hr))			Normalized metabolic rate		Exponent	Citation for exponent
	Mouse	Rat	Dog	Mean	SD		
Blood	0.06	0.025	0.006	0	0	0.99	Prothero (1996)
Brain	3.09	1.84	1.37	0.535	0.084	0.75	Allman (1999)
Diaphragm	2.33	1.8		0.444	0.016	0.865	Mathieu et al. (1981)
Fat	0.43		0.26	0.089	0.02	1.146	Prothero (1995)
Heart	1.29	1.93	0.75	0.338	0.113	0.98	Prothero (1979)
Kidney	5.04	4.12	2.47	1	0	0.85	Prothero (1984)
Liver	3.33	2.01	2.05	0.657	0.172	0.886	Prothero (1982)
Lungs	0.14	1.25	0.49	0.171	0.143	0.99	Stahl (1965)
Skeletal muscle	1.26	0.875	0.57	0.226	0.017	1	Stahl (1965)
Skeleton/bone	0.28	0.153	0.031	0.029	0.017	1.073	Prothero (1995)
Skin	0.48	0.416	0.17	0.082	0.015	0.92	Calder (1996)
Spleen	1.75	1.33	0.8	0.327	0.011	1.02	Stahl (1965)
Stomach/intestines	2.01		0.33	0.262	0.184	0.94	Adolph (1949)
Thyroid		1.18		0.225	0	0.92	Stahl (1965)

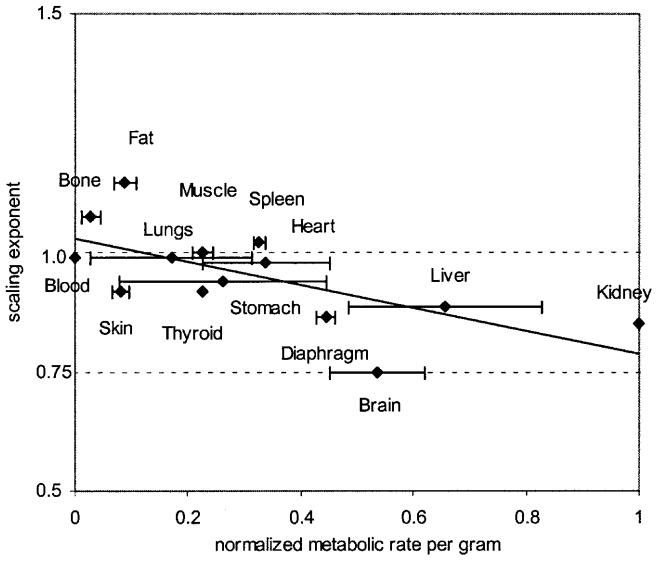

Fig. 5. Scaling exponent versus normalized metabolic rate per gram, taken from values in Table 2. For each organ, the scaling exponent is for M_{organ} as a function of body mass M. There is a significant correlation in the predicted direction ($R^2 = 0.4442$, $n = 14$, $p < 0.001$). Namely, organs with a greater normalized metabolic rate per gram tend to have exponents nearer to 3/4, and organs with lower normalized metabolic rate per gram tend to have exponents nearer to one. Horizontal error bars indicate standard deviation as shown in Table 2

Figure 5 shows how the scaling exponents vary as a function of normalized metabolic rate per gram. The plot is consistent with the prediction above: organs with greater normalized metabolic rate per gram (and thus greater capillary density) have exponents nearer to 3/4, and organs with lower normalized metabolic rate per gram (and thus lower capillary density) have exponents nearer to one. Thus, brain mass may scale against body mass with an exponent near 3/4 primarily because of these metabolic scaling considerations.

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