a0005 3.13 Scaling the Brain and Its Connections

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AU2 s0005 3.13.1 Introduction

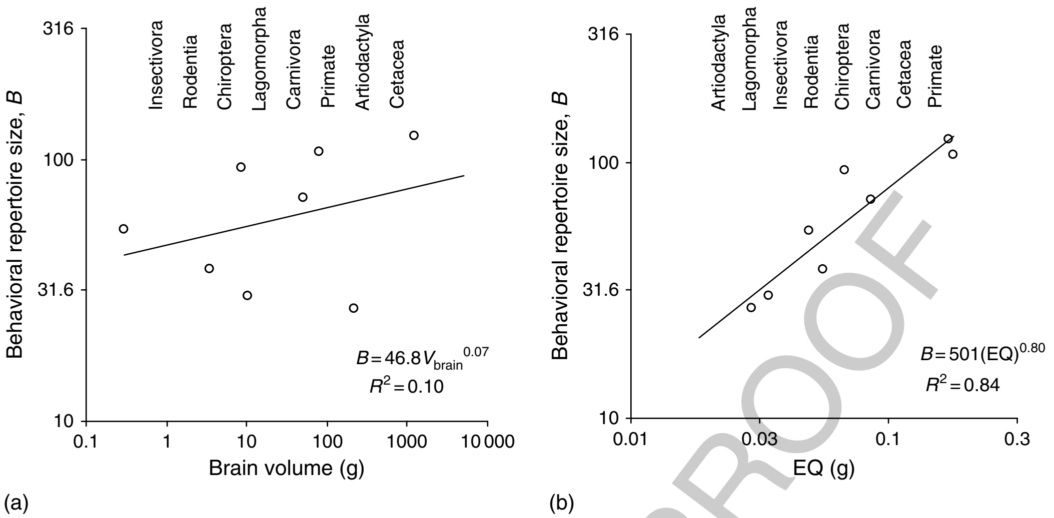
p0005 At first glance, larger brains seem more complex than smaller brains, having a greater number of synapses per neuron, greater surface convolutedness, more cortical areas, and disproportionately more white matter. However, brain size does not correlate with behavioral repertoire size as measured by ethologists (Figure 1), leading one to suspect that these seemingly increasingly complex features of larger brains are not underlying more complex computations. Instead, these seemingly complex features may be epiphenomenal consequences of making larger (not 'smarter') brains: it may be that a larger brain must satisfy certain invariant anatomical constraints that are fundamental to its function, and it is the satisfaction of these constraints in larger brains that leads to the seemingly complex features. In this light, the goal of studying how brains scale up in size across mammals is to identify the invariant anatomical constraints that are fundamental to brain function. Section 3.13.2 enumerates many of the neocortical changes that occur from small to large brains. Section 3.13.3 identifies key connectivity constraints that appear to be essential to brain function, no matter the size of the brain. In particular, these connectivity constraints are called 'invariant area-infiltration' and 'invariant area-interconnectedness,' summed up as 'invariant well-connectedness'. Section 3.13.4 explains how brains appear to satisfy these invariant connectivity constraints in an economical fashion, and that this is what explains why brains scale up in the broad manner that they do.

3.13.2 The Empirical Scaling Relationships s0010

In this section I review many of the changes the mammalian neocortex undergoes from small to large brains (see the third column of Table 1 for a summary). It must be recognized that these empirical scaling relationships are only zeroth-order descriptions of the neocortex, capturing neither ecology-dependent variation in brain organization nor important architectonic differences within brains. p0010

3.13.2.1 Number of Neurons, Synapse Density, Number of Synapses Per Neuron, Network Diameter s0015

One of the oldest neocortical scaling results is that the number of neocortical neurons, N, scales up disproportionately slowly compared to gray matter volume, V_{gray}, and in particular, $N \sim V_{\text{gray}}^{2/3}$ (b0485 Tower and Elliott, 1952; b0480 Tower, 1954; b0235 Jerison, 1973; b0405 Passingham, 1973; b0420 Prothero, 1997b). Alternatively, $V_{\text{gray}} \sim N^{3/2}$. Although the volumetric density of neurons therefore decreases, the volumetric density of synapses appears to remain approximately constant as a function of gray matter volume (b0005 Abeles, 1991). Together, these two scaling results entail that the average number of synapses per neuron, δ, increases as the 1/3 power of gray p0015

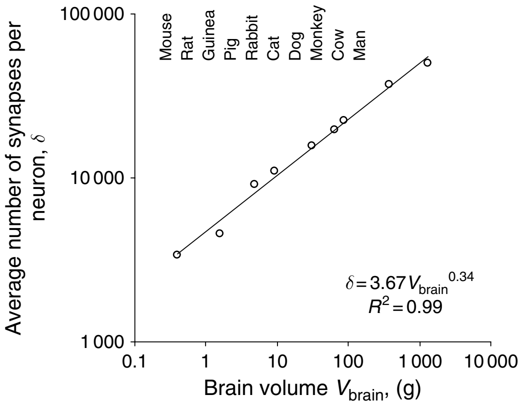


(a) (b)

f0005 **Figure 1** The neocortical scaling features are due to an increase in brain size, not due to an increase in behavioral complexity. This is because brain size does not correlate with behavioral repertoire size, as is shown in (a) which shows average behavioral repertoire sizes, B, for eight mammalian orders compiled from the ethology literature (Changizi, 2003a, 2003b) vs. brain volume, V_{brain} (averaged from animals measured in Hrdlicka (1907), Von Bonin (1937), Crile (1940), Stephan *et al.* (1981), the Stephan Collection, Hofman (1982), Haug (1987)). There is no significant correlation between them ($df = 6$, $t = 0.82$, $p > 0.2$). As is shown in (b), however, behavioral repertoire size 'does' increase as a function of the 'encephalization quotient', or EQ ($df = 6$, $t = 2.37$, $p < 0.05$). (EQ is brain mass (g) divided by the 3/4 power of body mass (g), which measures how big a brain is once one has corrected for how large the animal is; this is the appropriate normalization because brain mass increases as the 3/4 power of body mass.) The moral here is that the explanation for the neocortical scaling features probably will not appeal to increasing brain 'complexity'; instead, the explanation is likely to appeal to physico-mathematical constraints in making a larger – but not necessarily 'smarter' – brain.

t0005 **Table 1** Empirical and predicted (via the economical well-connectedness hypothesis) scaling exponents for a variety of neocortical quantities as a function of the number of neurons, N (top), and as a function of gray matter volume, V_{gray} (bottom). The 'formula' column shows the predicted exponent, parameterized by the parameter α, where $A \sim W^{\alpha}$. The final three columns show the predicted scaling exponent for three specific values of α: $\alpha = 1$, where the number of areas scales up as fast as possible (consistent with the well-connectedness constraints); $\alpha = 0.76$, the value of α that leads to the total wire volume scaling up as slowly as possible; $\alpha = 0$, where the number of areas remains constant as a function of brain size

				Optimal		
X		*Empirical*	*Formula*	$\alpha = 1$	$\alpha = 0.76$	$\alpha = 0$
Exponent z in $X \sim N^z$						
No. of connections per neuron	δ	≈ 0.5	$1/(1+\alpha)$	0.500	0.568	1.000
Axon radius	R	≈ 0.167	$1/(3+3\alpha)$	0.167	0.189	0.333
Gray matter volume	V_{gray}	≈ 1.5	$(2+\alpha)/(1+\alpha)$	1.500	1.568	2.000
Surface area	S	≈ 1.33	$(5+3\alpha)/(3+3\alpha)$	1.333	1.379	1.667
Thickness	T	≈ 0.167	$1/(3+3\alpha)$	0.167	0.189	0.333
White matter volume	V_{white}	$\approx 1.77 - 2$	$(7\alpha+4)/(3\alpha+3)$	1.833	1.765	1.333
No. of area-connections per area	D	≈ 0.5	$\alpha/(1+\alpha)$	0.500	0.432	0.000
No. of neurons per area	W	≈ 0.5	$1/(1+\alpha)$	0.500	0.568	1.000
No. of areas	A	≈ 0.5	$\alpha/(1+\alpha)$	0.500	0.432	0.000
Exponent z in $X \sim V_{\text{gray}}^{z}$						
No. of neurons	N	≈ 0.67	$(1+\alpha)/(2+\alpha)$	0.667	0.638	0.500
Axon radius	R	≈ 0.1	$1/(6+3\alpha)$	0.111	0.121	0.167
No. of connections per neuron	δ	≈ 0.33	$1/(2+\alpha)$	0.333	0.362	0.500
Surface area	S	≈ 0.9	$(5+3\alpha)/(6+3\alpha)$	0.889	0.879	0.833
Thickness	T	≈ 0.1	$1/(6+3\alpha)$	0.111	0.121	0.167
White matter volume	V_{white}	$\approx 1.15 - 1.33$	$(7\alpha+4)/(3\alpha+6)$	1.222	1.126	0.667
No. of area-connections per area	D	≈ 0.33	$\alpha/(2+\alpha)$	0.333	0.275	0.000
No. of neurons per area	W	≈ 0.33	$1/(2+\alpha)$	0.333	0.362	0.500
No. of areas	A	≈ 0.33	$\alpha/(2+\alpha)$	0.333	0.275	0.000



AU2a f0010 **Figure 2** The average number of synapses per neuron, δ, scales as the 1/3 power of gray matter volume, V_{gray}. The plot shows the average number of synapse per neuron, δ, vs. brain volume, V_{brain}. The synapse numbers are computed using data from [b0485] Tower and Elliott (1952), who present data for how neuron density decreases in larger brains (namely, it decreases as the $-1/3$ power of brain volume). Since volumetric synapse density remains invariant as a function of brain size ([b0005] Abeles, 1991; [b0065] Changizi, 2001b), a neuron density decrease corresponds to a proportional increase in the number of synapses per neuron. The synapse values were computed assuming that the average number of synapses per neuron in human is 50 000; this choice of 50 000 serves to set the proportionality constant, but does not effect the scaling exponent. In addition to concluding that $\delta \sim V_{\text{gray}}^{1/3}$, it also follows that $\delta \sim N^{1/2}$, where N is the total number of neocortical neurons. (This plot shows brain volume along the x-axis, not gray matter volume, but measured exponents for gray matter volume vs. brain volume are approximately one: 0.983 ([b0415] Prothero, 1997a), 0.982 ([b0220] Hofman, 1991), 1.054 ([b0215] Hofman, 1989), 1.04 ([b0425] Prothero and Sundsten, 1984), 1.06 ([b0185] Frahm *et al.*, 1982), and 1.08 ([b0240] Jerison, 1982). For this reason, it is empirically justified to use brain volume as a proxy for gray matter volume, and this is done in some upcoming figures as well.).

matter volume; that is, $\delta \sim V_{\text{gray}}^{1/3}$ (see Figure 2). Or, as a function of the number of neurons, $\delta \sim N^{1/2}$.

p0020 Interestingly, although the number of synapses per neuron scales up considerably more slowly than the number of neurons, the scaling is sufficiently fast to maintain a low network diameter (i.e., the average number of axons that must be traversed to get from any neuron to another): assuming that the neocortex is small-world (i.e., having sufficiently many axons connecting otherwise-separated parts of neocortex that the network diameter can be approximated as that of a random network), the network diameter may be approximated as $\Lambda \approx (\log N)/(\log \delta)$, which manipulates to $\Lambda \approx 2 \times [1 + (\log c)/(\log N)]$, where c is the proportionality constant in the equation $\delta = cN^{1/2}$ ([b0065] Changizi, 2001b). For sufficiently large brains, Λ approaches 2; also, estimates of c are on the order of 1, meaning that perhaps the network diameter is AU3 $\Lambda \approx 2$ in actual neocortices.

3.13.2.2 Surface Area, Thickness, Minicolumns, and Columns s0020

p0025 The neocortical gray matter is a sheet on the outside of the brain (with white matter axons filling the center). There are neuroanatomical structures called minicolumns extending through the thickness of the neocortical gray matter from pia to white matter ([b0385] Mountcastle, 1957, [b0390] 1997; [b0475] Tommerdahl *et al.*, 1993; [b0410] Peters, 1994; [b0245] Jones, 2000), and the number of neurons in a minicolumn (i.e., along a thin line through the thickness of gray matter) appears to be approximately invariant (on the order of 100) as a function gray matter volume ([b0440] Rockel *et al.*, 1980; [b0420] Prothero, 1997b, Changizi, 2001b). Because of the neuron density decrease discussed earlier (namely neuron density $\rho_{\text{neuron}} \sim V_{\text{gray}}^{-1/3}$), it follows that gray matter thickness, T, must increase as the 1/9 power of gray matter volume, $T \sim V_{\text{gray}}^{1/9}$, and indeed this is what has been measured ([b0210] Hofman, 1985, [b0215] 1989, [b0220] 1991; [b0240] Jerison, 1982; [b0425] Prothero and Sundsten, 1984; [b0415] Prothero, 1997a). Because gray matter volume is equal to its surface area, S, times its thickness, T, it also follows immediately that $S \sim V_{\text{gray}}^{8/9}$, something also measured (ibid.). AU4 Surfaces of geometrically similar objects scale as the 2/3 power of volume, and the fact that this exponent of approximately 8/9 is greater than 2/3 means that the neocortex surface cannot remain geometrically identical as the brain enlarges, but must, instead, become increasingly convoluted, as it does in larger brains. We see, then, that gray matter thickness and surface area scaling follow from (1) the neuron density decrease in larger brains, and (2) the invariant number of neurons in a minicolumn.

p0030 Minicolumns are not the only anatomical structure in gray matter that appears to have an invariant number of neurons: the number of neurons in a neocortical 'module' (such as columns, blobs, barrels, stripes) also does not appear to vary as a function of gray matter volume (see [b0075] Changizi (2003b), using data from [b0365] Manger *et al.* (1998)). Such fundamental invariant-sized structures are found in a wide variety of complex network, and may be invariant in size for reasons of economical scaling (see [b0095] Changizi *et al.* (2002), Changizi (2003b), Changizi and He 2005)).

3.13.2.3 Axon Caliber and White Matter Volume s0025

p0035 We saw earlier that the number of synapses per neuron, δ, scales as the 1/3 power of gray matter volume (or as the square root of the number of neurons). Biological structures with more 'leaves' are almost always supported by thicker 'trunks', and we should therefore expect that as the number of synapses per neuron increases, axon calibers and soma diameters should increase. Indeed, white matter axon caliber, R, appears to increase in size in larger brains (Harrison *et al.*, 2002), and, in particular, approximately as the 1/9 power of gray matter volume, $R \sim V_{\text{gray}}{}^{1/9}$ (Shultz and Wang, 2001). (Soma diameter for spinal motor neurons also scales approximately as the 1/9 power of gray matter volume (Changizi, 2001b).) It follows that axon caliber scales as the 1/3 power of the number of synapses per neuron, $R \sim \delta^{1/3}$, or $R^3 \sim \delta$. Because volumetric synapse density is invariant as a function of gray matter volume (see Section 3.13.2.1 above), the linear dimensions of synapses must be invariant, and the relationship $R^3 \sim \delta$ can be rewritten as $R^3 \sim \delta \times R_{\text{synapse}}{}^3$, where R_{synapse} is the linear dimensions of a synapse. This equation is a version of Murray's law (Murray, 1926), which is an optimality principle relating a parent branch caliber to the caliber of its daughter segments, and is approximately consistent with the parent–daughter diameters of a wide variety of kinds of neural arbor (Cherniak *et al.*, 1999; Chklovskii and Stepanyants, 2003).

p0040 White matter volume, V_{white}, follows from the above scaling exponents as explained below. Assuming the number of white matter projecting neurons, N_{white}, scales proportionally to the total number of neurons, N, $V_{\text{white}} \sim N \times L \times R^2$, where L is the average length traveled by a white matter axon, and R is the caliber of a white matter axon. We saw earlier that $N \sim V_{\text{gray}}{}^{2/3}$ and $R \sim V_{\text{gray}}{}^{1/9}$. If L is taken to be the linear dimensions of the gray matter, then $L \sim V_{\text{gray}}{}^{1/3}$, and $V_{\text{white}} \sim V_{\text{gray}}{}^{11/9}$. If, however, L is taken to be the linear dimensions of the white matter, then $L \sim V_{\text{white}}{}^{1/3}$, and some algebraic manipulation leads to $V_{\text{white}} \sim V_{\text{gray}}{}^{4/3}$ (Changizi, 2001b). Indeed, measured exponents tend to be around 1.2–1.3 (Frahm *et al.*, 1982; Hofman, 1989, 1991; Allman, 1999; Zhang and Sejnowski, 2000; Bush and Allman, 2003). White matter volume, then, scales up disproportionately quickly as a function of gray matter volume, and this is due to white matter axon caliber increasing as it does (and this, in turn, is due to the increasing number of synapses per neuron): if white matter axon caliber were constant, then white matter volume would scale proportionally with gray matter volume (Changizi, 2001b).

s0030 3.13.2.4 Number of Areas and Number of Area-Connections per Area

p0045 The neocortex is partitioned into functionally distinct 'areas', an area which is a contiguous anatomical region involved in some suite of related computations. The labs of Kaas, Krubitzer, and colleagues have determined the boundaries of many areas in a wide variety of mammals, and by compiling results from their studies it is possible to estimate the total number of areas across 19 mammals of varying brain size (see Figure 3). The number of areas, A, scales approximately as the 1/3 power of gray matter volume, $A \sim V_{\text{gray}}{}^{1/3}$, or $A \sim N^{1/2}$ (Changizi, 2001b, Changizi, 2003b, Changizi and Shimojo, 2005). It follows that the average number of neurons per area, W, also scales as the 1/3 power of gray matter volume, $W \sim V_{\text{gray}}{}^{1/3}$, or $W \sim N^{1/2}$. Note that although the 'average' number of neurons per area scales as the 1/3 power of gray matter volume, some areas such as V1 and V2 appear to violate this average tendency, scaling as the 2/3 power of gray matter volume, or proportional to the total number of neurons (Changizi and Shimojo, 2005).

Areas connect to other areas via white matter axons, and the average number of areas to which p0050

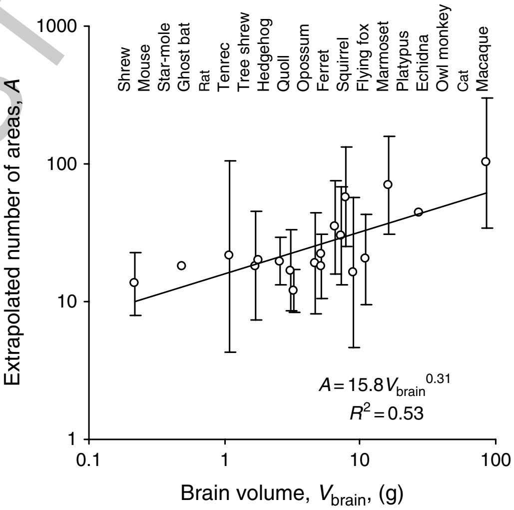
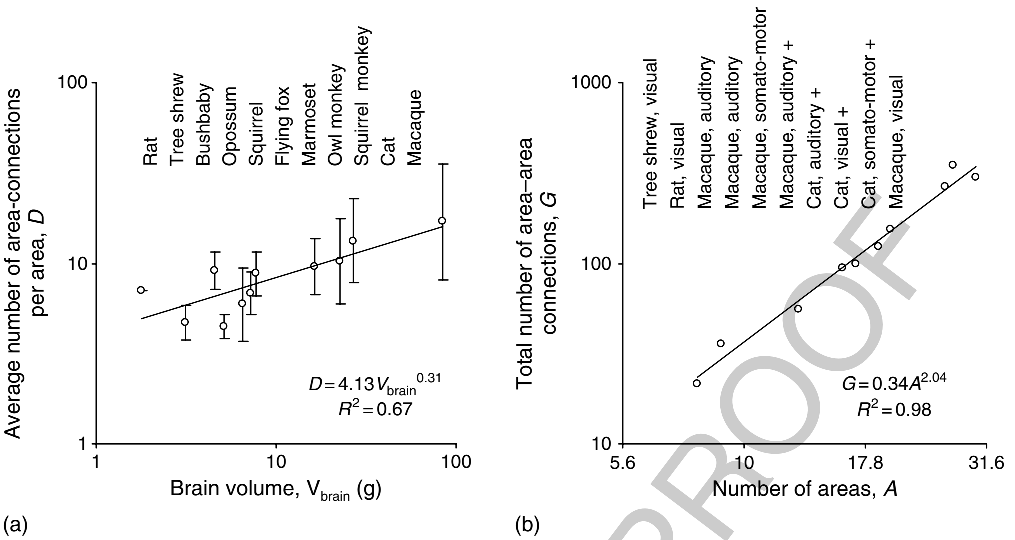


Figure 3 The number of cortical areas, A, and the average number of neurons per area, W, each scale as the 1/3 power of gray matter volume, V_{gray}. The plot shows the extrapolated number of cortical areas, A, vs. brain volume, V_{brain}. (Standard deviation bars are shown.) For each of 19 mammals studied by Kaas, Krubitzer, and colleagues, the average fraction of neocortex taken up by a cortical area was measured (Changizi and Shimojo, 2005). For example, if the average neocortical area takes up 5% of the neocortex, then the extrapolated total number of areas is 1/0.05 = 20. The 'extrapolated number of areas' is the inverse of this fraction. The data are from the following papers: Catania *et al.* (1999), Krubitzer and Huffman (2000), Krubitzer (1995), Northcutt and Kaas (1995), Krubitzer *et al.* (1995, 1997), Lyon *et al.* (1998), Beck *et al.* (1996), Manger *et al.* (2002), Kaas (1987). The best-fit scaling exponent is 0.31 (95% confidence interval is (0.16, 0.46)), or approximately $A \sim V_{\text{gray}}{}^{1/3}$. The average number of neurons per area, W, can be computed from this as follows: $W = N/A$, where N is the total number of neocortical neurons. The total number of neocortical neurons scales as the 2/3 power of brain volume, so $W \sim (V_{\text{brain}}{}^{2/3})/(V_{\text{brain}}{}^{0.31}) = V_{\text{brain}}{}^{0.36}$, or approximately $W \sim V_{\text{brain}}{}^{1/3}$. Note also that this means A and W each scale approximately as the 1/2 power of the number of neurons, N. f0015



f0020 **Figure 4** The average number of area-connections per area, D, scales as the 1/3 power of gray matter volume, V_{gray}. (a), plot of the average number of area-connections per area, D, vs. brain volume, V_{brain} (standard deviation bars shown) for 12 mammals accumulated from approximately one dozen articles in the literature (see Changizi and Shimojo (2005)). For each animal, the number of area-connections has typically been measured within the literature only for a relatively small number of areas, and usually from visual or somatosensory areas. The data are from the following papers: Kahn *et al.* (2000), Beck *et al.* (1996), Lyon and Kaas (2001, 2002a, 2002b), Beck and Kaas (1998), Krubitzer and Kaas (1990a, 1990b), Collins *et al.* (2001), Lyon *et al.* (1998), Fabri and Burton (1991), Krubitzer *et al.* (1986, 1993), Kaas *et al.* (1989), Scannell *et al.* (1995), Lewis and Van Essen (2000). The best-fit scaling exponent is 0.31 (95% confidence interval is (0.145, 0.468)), so that it is approximately the case that $D \sim V_{gray}^{1/3}$ (and $D \sim N^{1/2}$). (b), plot of the total number of area(area connections, G, vs. the number of areas, A, in 'area-subnetworks' of tree shrew, rat, cat, and macaque (Changizi, 2003b; Changizi and Shimojo, 2005). These data were compiled from the following papers: Lyon *et al.* (1998), Coogan and Burkhalter (1993), Hackett *et al.* (1998), Young (1993), Kaas and Hackett (2000), Scannell and Young (1993). The best-fit scaling exponent is 2.04 (95% confidence interval is (1.807, 2.263)), or approximately $G \sim A^2$. Because the total number of area(area connections, $G = A \times D$, we can derive that $D \sim A$. Recalling that $A \sim V_{gray}^{1/3}$, we conclude again that $D \sim V_{gray}^{1/3}$ (and $D \sim N^{1/2}$).

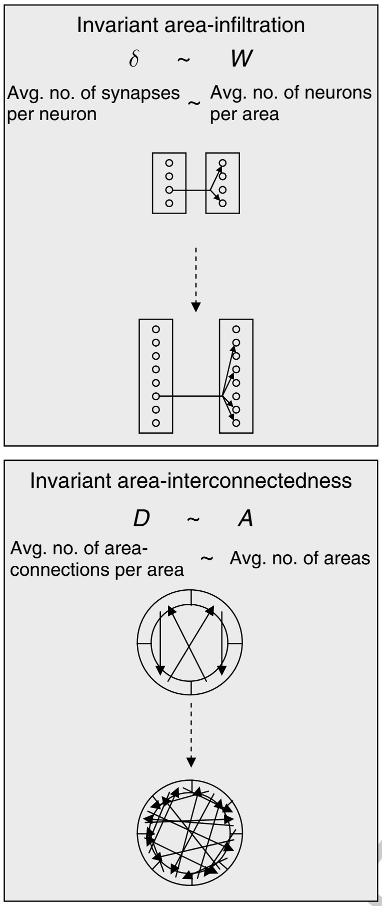
an area connects (or, the average number of area-connections per area), D, scales approximately proportional to the 1/3 power of gray matter volume (Changizi and Shimojo, 2005), that is, $D \sim V_{gray}^{1/3}$, or $D \sim N^{1/2}$ (Figure 4). This can be shown by measurements of the average number of area-connections per area across a variety of studied areas (mostly visual and somatosensory) in a variety of mammals (Figure 4a), and also by measuring the total number of area-connections in 'area-subnetworks' within tree shrew, rat, cat, and macaque (Figure 4b). These area and area-connection scaling relationships are consistent with the "square-root compartment" conjecture by Braitenberg (Braitenberg, 1978, 2001; Braitenberg and Schuz, 1998).

s0035 3.13.3 Two Fundamental Connectivity Constraints: Invariant Well-Connectedness

p0055 Two surprising and important implications concerning connectivity spring from the variety of scaling exponents discussed in Section 3.13.2.

3.13.3.1 Invariant Area-Infiltration s0040

p0060 The first important observation concerning connectivity is that both the average number of synapses per neuron, δ (Figure 2), and the average number of neurons per area, W (Figure 3), scale approximately as the 1/3 power of gray matter volume (or as the square root of the total number of neocortical neurons). Therefore, $\delta \sim W$, that is, the average number of synapses per neuron scales are approximately directly proportional to the average number of neurons per area. AU5 When a neuron makes connections within an area, the number of synapses it makes is, on average, some invariant fraction of the number of neurons in the area (Figure 5a,). This invariance property is referred to as 'invariant area-infiltration', because, independent of brain size, neurons have, on average, sufficiently numerous synapses to 'infiltrate' an invariant fraction of the neurons in an area. In humans, the average number of synapses per neuron, δ, is on the order of 10^4–10^5 and the average number of neurons per area, W, is on the order of 10^8 (given $N \approx 10^{10}$ neurons and $A \approx 100$ areas), and thus $\delta \approx cW$, where the proportionality constant is $c \approx 10^{-4}$–10^{-3}. On average, neurons



f0025 **Figure 5** Two fundamental connectivity invariants found in the mammalian neocortex, summarized as ‘invariant well-connectedness’. The first is ‘invariant area-infiltration’, which is the empirical observation that the average number of synapses per neuron, δ, scales approximately directly proportionally with the number of neurons per area, *W*. (Namely, each of these quantities scales approximately as the 1/3 power of gray matter volume (see Figures 2 and 3)). The second is ‘invariant area-interconnectedness’, which is the empirical observation that the average number of area-connections per area, *D*, scales approximately directly proportionally with the number of areas, *A*. (Namely each of these quantities scales approximately as the 1/3 power of gray matter volume (see Figures 3 and 4)).

connect on the order of 10^{-4}–10^{-3} of the neurons in an area, independent of the number of neurons in an AU6 areas.

s0045 3.13.3.2 Invariant Area-Interconnectedness

p0065 The second important observation concerning connectivity is that both the average number of area-connections per area, *D* (Figure 4), and the number of areas, *A* (Figure 3), scale approximately as the 1/3 power of gray matter volume (or as the square root of the total number of neocortical neurons). Therefore, $D \sim A$, that is, the average number of area-connections per area scales approximately directly proportionally to the number of areas (Figure 5b). Equivalently, the total number of area-connections scales approximately as the square of the number of areas (something we saw in Figure 4b). This invariance property is referred to as ‘invariant area-interconnectedness’. The proportionality constant in $D \approx cA$ may be estimated from Figure 4b, which is $c \approx 0.34$, that is, each area connects to approximately 1/3 of the areas in neocortex, independent of the number of areas (although this is likely to be an overestimate because Figure 5 is for subnetworks which are probably more highly interconnected than is the entire neocortex).

3.13.3.3 Invariant Well-Connectedness s0050

The mammalian neocortex appears to satisfy both p0070 connectivity invariances mentioned above – invariant area-infiltration and invariant area-interconnectedness – and joint satisfaction of these is referred to as invariant well-connectedness. Maintaining invariant neuron-interconnectedness for the entire neocortex (i.e., where the average number of synapses per neuron would scale proportionally to the total number of neocortical neurons) would be exorbitantly expensive ([b0170]Deacon, 1990; [b0470]Stevens, 1989; [b0430]Ringo, 1991), and so, instead, the mammalian neocortex takes a two-tiered approach: (1) invariant neuron-interconnectedness ‘within areas’ (i.e., invariant area-infiltration), and (2) invariant area-interconnectedness among areas in the entire neocortex. Satisfaction of these two invariances is inexpensive relative to maintenance of invariant neuron-interconnectedness for the entire neocortex. Invariant area-infiltration appears to be due to a requirement that some minimum level of interconnectivity be achieved ‘within’ areas in order for areas to properly function. And invariant area-interconnectedness appears to be due to a requirement that some minimum level of interconnectivity be achieved ‘between’ areas in order for the entire neocortex to properly function. There is, however, currently no explanation for why mammalian brains have been selected to conform to these invariances. Nor is there an explanation for why there are two tiers, and not more.

3.13.4 Economical Neocortex s0055

Thus far, I have reviewed the empirical scaling rela- p0075 tionships (Section 3.13.2) and identified two important connectivity invariance principles that govern neocortical scaling (Section 3.13.3). However, I have not yet provided an explanation for why the neocortex scales up in the ways that it does. Although, as mentioned above, I have no explanation for why the mammalian neocortex conforms to the principle of invariant well-connectedness, might it be that 'given' that the mammalian neocortex must (for some reason) conform to this principle, 'then' the other neocortical scaling features follow? The answer is 'no': satisfaction of invariant well-connectedness does 'not' entail the other scaling exponents, for there are multiple possible ways of scaling a brain while satisfying invariant well-connectedness. In particular, invariant well-connectedness only states that $\delta \sim W$ (invariant area-infiltration) and $D \sim A$ (invariant area-interconnectedness); it does not say how the average number of neurons per area, W, and the number of areas, A, relate to one another.

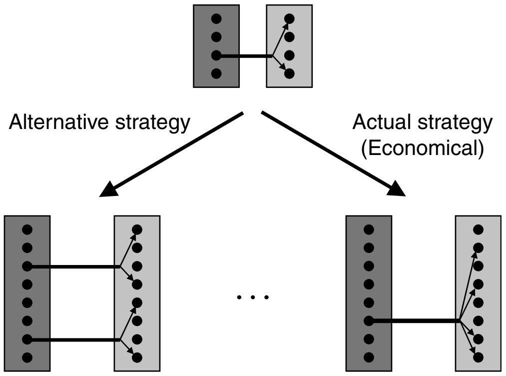
p0080 In fact, W and A scale approximately proportionally to one another (each scales approximately as the 1/3 power of gray matter volume, or as the square root of the number of neocortical neurons), and it suffices to explain this, and the other scaling exponents then do follow. Although invariant well-connectedness does not entail the proportional relationship between W and A, if we hypothesize that the neocortex is selected to satisfy invariant well-connectedness in a volume-optimal manner – 'economical well-connectedness' – then it *is* possible to explain why it is approximately the case that $W \sim A$. There is considerable evidence to date that there is strong selective pressure for "wire-optimality" in the brain (Cajal, 1995; Kaas, 1977, 1989, 1995, 1997, 2000; Cowey, 1979, 1981; Barlow, 1986; Durbin and Mitchison, 1990; Mitchison, 1991, 1992; Ringo, 1991; Ringo *et al.*, 1994; Cherniak, 1992; Young, 1992; Traverso, 1992; Jacobs and Jordan, 1992; Ruppin *et al.*, 1993; Cherniak, 1994, 1995; Van Essen, 1997; Cherniak *et al.*, 1999; Chklovskii, 2000; Chklovskii and Koulakov, 2000; Changizi, 2001a; Changizi *et al.*, 2002; Chklovskii *et al.*, 2002; Changizi, 2003b; Klyachko and Stevens, 2003; Cherniak *et al.*, 2004; Changizi and He, 2005; Changizi, under review).

p0085 Changizi (2001b) presented a simple argument for why economical satisfaction of well-connectedness would explain $W \sim A$ (i.e., the number of neurons per area scaling proportionally with the number of areas). Namely, a greater number of synapses per neuron, δ, will tend to lead to a greater amount of volume devoted to 'wiring' (because more synapses per neuron requires more arborization and thicker 'trunks' supporting the arbor). Therefore, we would expect the number of synapses per neuron to scale up as slowly as possible, so long as well-connectedness remains satisfied. Because the number of synapses per neuron must scale proportionally to the number of neurons per area (i.e., $\delta \sim W$, or invariant area-infiltration), wire-economy consequently expects the number of neurons per area, W, to scale up as slowly as possible. The slowest that the number of neurons per area can scale up is proportional to the number of areas, because (by invariant area-interconnectedness) each area must have sufficiently enough neurons to connect to an invariant proportion of the total number of areas. So, the number of neurons per area must scale proportionally with the total number of areas, that is, $W \sim A$.

This argument above relies on the simple heuristic 'fewer synapses per neuron tends to entail lower overall wiring volume', and from it and the hypothesis of well-connectedness one can derive $W \sim A$ (and all the scaling relationships discussed earlier). However, this heuristic hides the fact the total volume of wire in the neocortex depends not only on the number of synapses per neuron, but also on how far neurons must reach. For the remainder of this section I put forth a more rigorous derivation of how wiring volume depends on different scaling strategies relating W and A. We will see that wiring optimality does indeed predict that W and A should scale approximately proportionally to one another, just as the simple heuristic argument predicted. The contents of the remainder of this section are somewhat more mathematical, and if one is content with the heuristic argument above, one may jump to the next section. p0090

3.13.4.1 Economical Satisfaction of Invariant Area-Infiltration s0060

Before explaining more rigorously why it is volume-optimal for the average number of neurons per area, W, to scale proportionally with the number of areas, – which is key to deriving the other scaling exponents – it is useful to see that invariant-infiltration itself is volume-optimal (see Figure 6). Suppose an area needs to infiltrate the neurons in some other area. One extreme strategy – the actual strategy – is to, as the number of neurons per area, W, increases, have a fixed number of neurons carry out the infiltration, but have the number of synapses per neuron, δ, increase proportionally with W. If M is the number of neurons in the area responsible for the infiltration, then for the actual strategy, $M \sim W^0$ and $\delta \sim W$. The other extreme strategy is to keep δ invariant as W increases, and increase the number of neurons doing the infiltration proportionally with W; for this alternative strategy, $M \sim W$ and $\delta \sim W^0$. More generally, suppose that $M \sim W^\beta$, where β is a constant from 0 to 1. p0095



f0030 **Figure 6** Illustration that the actual scaling strategy for invariant area-infiltration is volume-optimal. The neocortex across mammals appears to economically maintain a constant degree of area-infiltration, no matter the size of the areas, where 'area-infiltration' is the fraction of neurons in an area to which a neuron connects. On the right is shown the actual scaling strategy, where when the number of neurons per area is doubled, the number of neurons connecting from one area to the other remains the same, and the number of connections per neuron is doubled. The neural volume required is $V_{\mathrm{actual}} = LR_{\mathrm{actual}}^2$, where L is the distance between the areas, and R_{actual} is the caliber of a white-matter axon. From Murray's law (see Section 3.12.2.3), $R \sim \delta^{1/3}$, where δ is the number of synapses per neuron, and so $V_{\mathrm{actual}} \sim L\delta_{\mathrm{actual}}^{2/3}$. Since $\delta_{\mathrm{actual}} = 4$ in this illustration, $V_{\mathrm{actual}} \sim L4^{2/3} = L2^{4/3}$ On the left is shown an alternative strategy, where when the number of neurons per area is doubled, the number of neurons connecting from one area to the other doubles, and the number of connections per neuron remains the same. The neural volume required for this strategy is $V_{\mathrm{altern}} = 2LR_{\mathrm{altern}}^2$, where the '2' in front is due to there now being two white matter axons in the illustration, rather than one. From Murray's law, $V_{\mathrm{altern}} \sim 2L\delta_{\mathrm{altern}}^{2/3}$, and since $\delta_{\mathrm{altern}} = 2$, $V_{\mathrm{altern}} \sim 2L2^{2/3} = L2^{5/3}$. Therefore, $V_{\mathrm{altern}} = 2^{1/3}V_{\mathrm{actual}}$, and the actual strategy is cheaper.

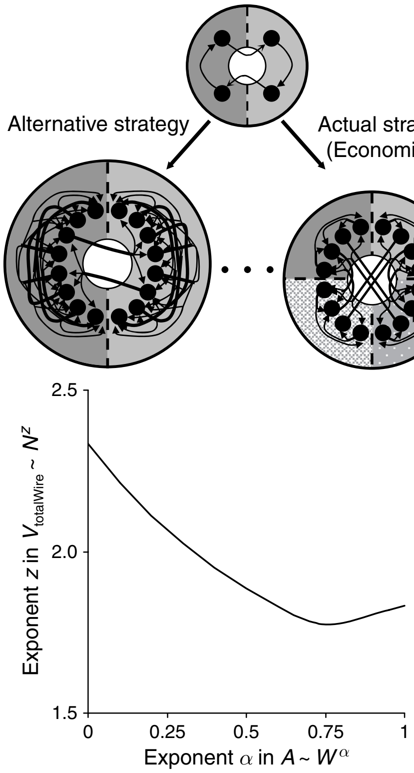
$\beta = 1$ corresponds to the actual scaling strategy for infiltration, and $\beta = 0$ corresponds to the opposite extreme. To infiltrate the area, it must be that $M\delta \sim W$. It follows that $\delta \sim W^{1-\beta}$. The volume of wire required to implement the infiltration is given by $V = MLR^2$, where L is the distance required for the connection, and R is the axon caliber. As discussed in Section 3.13.2.3, $R \sim \delta^{1/3}$, and thus we have $R \sim W^{(1-\beta)/3}$. The volume of wire can be written now as $V \sim LW^{\beta}W^{2(1-\beta)/3} = LW^{(2+\beta)/3}$. Assuming that L is the same under any of the alternative scenarios, V scales up most slowly when β is minimal, namely at $\beta = 0$, corresponding to the case where $\delta \sim W$, the actual case found in the neocortex (see Section 3.13.3.1). AU7 That is, the most economical way for an area to infiltrate another is to send a constant number of neurons, and have the number of connections per neuron increase proportionally with the number of neurons in the area; *not* to increase the number of neurons in the area devoted to connecting to an area. Also, when combined with the invariant area-interconnectedness constraint, we can conclude that the total number of white matter neurons per area, W_{white}, is expected to scale proportionally with the number of cortical areas, A; that is, $W_{\mathrm{white}} \sim A$. We will utilize this result below in our further theoretical development.

3.13.4.2 Economical Satisfaction of Invariant Well-Connectedness s0065

p0100 AU8 We now consider the possible ways of parcellating the neocortex. At one extreme, there could be a fixed number of cortical areas, A, and the number of neurons per area, W, would scale directly proportionally with the total number of neurons (Figure 7, left side). In this case, $A \sim W^0$. At the other extreme, the fastest the number of areas can increase is proportionally with the number of neurons per area (Figure 7, right side), because invariant area-interconnectedness requires that there be enough neurons per area to connect to an invariant fraction of the total number of areas. In this case, $A \sim W$. Generally, this space of scaling possibilities is given by $A \sim W^{\alpha}$, where α ranges from 0 to 1 (see the x-axis of Figure 7).

p0105 Which value of α should we expect for the neocortex? The 'economical' hypothesis is that the manner of scaling up the number of areas – that is, the setting of the parameter α – is such that the total neuronal wiring volume scales up as slowly as possible (subject to the satisfaction of the invariant well-connectedness constraint). The total volume of wire, $V_{\mathrm{totalWire}}$, can be split into the volume of intra-area wire, $V_{\mathrm{intraWire}}$, and the volume of white matter, $V_{\mathrm{whiteWire}}$; that is, $V_{\mathrm{totalWire}} = V_{\mathrm{intraWire}} + V_{\mathrm{whiteWire}}$. The volume of intra-area wire is given by $V_{\mathrm{intraWire}} = (N_{\mathrm{intra}})(L_{\mathrm{intra}})(R_{\mathrm{intra}})^2$, where N_{intra} is the total number of neocortical neurons involved in intra-area connections, L_{intra} is the average length of an intra-area connection, and R_{intra} is the average caliber radius of the major axon for intra-area connections. Similarly, the volume of white matter is given by $V_{\mathrm{whiteWire}} = (N_{\mathrm{white}})(L_{\mathrm{white}})(R_{\mathrm{white}})^2$. We would like to write $V_{\mathrm{totalWire}}$ as a function of the total number of neurons, N, and the parameter α, so that we may determine the value of α that minimizes the scaling rate for $V_{\mathrm{totalWire}}$. By utilizing the two well-connectedness constraints, along with our earlier observations concerning optimal area-infiltration, we will be able to write each of the terms above – N_{intra} and N_{white}, R_{intra} and R_{white}, and L_{intra} and L_{white} – as a function of N and α.

p0110 N_{intra} *and* N_{white}. The total number of white matter neurons, N_{white}, is equal to the number of white matter neurons per area, W_{white}, times the total number of areas, A; that is, $N_{\mathrm{white}} = (A)(W_{\mathrm{white}})$.



f0035 **Figure 7** Illustration that the actual scaling strategy for invariant well-connectedness is near volume-optimal. To maintain invariant well-connectedness, area-infiltration (the fraction of neurons in an area to which a neuron connects) *and* area-interconnectedness (the percentage of areas in the neocortex to which an area connects) must remain constant as brain size increases. On the right is shown the actual scaling strategy, where when the number of neurons in the brain, N, quadruples (from 4 to 16), the number of areas, A, approximately doubles (from 2 to 4), i.e., $A \sim N^{1/2}$. For this case, the number of areas scales proportionally with the number of neurons per area, W, the latter which also doubles (from 2 to 4), i.e., $A \sim W^{\alpha}$, where $\alpha = 1$. Invariant area-infiltration is satisfied by doubling the number of neurons to which each neuron (both inter-area and intra-area) connects (from 1 to 2). Invariant area-interconnectedness is achieved by doubling the number of areas to which each area connects (from 1 to 2). This actual scaling strategy can be summarized by the exponent $\alpha = 1$, which leads (see Section 3.13.4.2) to the total volume of wire scaling as $V_{\text{totalWire}} \sim N^z$, where $z = 11/6 = 1.83$; this is shown in the plot (bottom) of the exponent z as a function of α. On the left is shown an alternative strategy, where when the number of neurons in the brain quadruples (from 4 to 16), the number of areas remains constant (at 2). The relationship between the number of areas and number of neurons per area is therefore $A \sim W^{\alpha}$, where now $\alpha = 0$. For this case, invariant area-infiltration is satisfied by quadrupling the number of neurons to which each neuron connects (from 1 to 4). Invariant area-interconnectedness is achieved by having each area connect to just one other area, just as in the smaller brain. This alternative scaling strategy can be summarized by this exponent $\alpha = 0$, which leads to the total volume of wire scaling as $V_{\text{totalWire}} \sim N^z$, where $z = 7/3 = 2.33$; this is shown in the plot (bottom) of the exponent z as a function of α. The exponent $z = 2.33$ for the alternative scaling strategy is very significantly higher than the $z = 1.83$ for the actual scaling strategy, and the latter exponent is near the optimal of 1.765 occurring at $\alpha = 0.76$. See Section 3.13.4.2 for the more general derivation.

By virtue of the optimality argument discussed in the previous section, the number of white matter neurons per area must scale in proportion with the total number of areas; that is, $W_{\text{white}} \sim A$. Thus, we may write $N_{\text{white}} \sim A^2$. We also know that the total number of neurons, $N = WA$ (where W is the average number of neurons per area), and along with the α power law relationship, $A \sim W^{\alpha}$, we have that $N \sim (A^{1/\alpha})(A)$, or $A \sim N^{\alpha/(1+\alpha)}$. Therefore, $N_{\text{white}} \sim N^{2\alpha/(1+\alpha)}$. Also, $N_{\text{intra}} = N - N_{\text{white}}$.

R_{intra} *and* R_{white}. We learned earlier (Section 3.13.2.3) that $R \sim \delta^{1/3}$, where R is the radius of an axon caliber. From this and invariant area-infiltration, $\delta \sim W$, we may write that $R \sim W^{1/3}$. Recalling the α power law relationship, $A \sim W^{\alpha}$, we have that $R \sim A^{1/(3\alpha)}$. We saw earlier that $A \sim N^{\alpha/(1+\alpha)}$, and thus $R \sim N^{1/[3(1+\alpha)]}$. We assume in this derivation that every neuron in the neocortex scales up proportionally with one another (in terms of the number of synapses per neuron), and therefore this proportionality relationship for R is valid for both R_{intra} and R_{white}. p0115

L_{intra} *and* L_{white}. The average length of an intra-area connection, L_{intra}, is given by the average linear dimensions of an area, $L_{\text{intra}} \approx (V_{\text{gray}}/A)^{1/3}$, where V_{gray} is the total volume of gray matter. Gray matter volume is modeled as scaling proportionally with the total number of synapses in the network. This is, in fact, true across actual mammalian neocortices, because synapse density does not vary with neocortex size (Abeles, 1991), so doubling the gray matter volume means doubling the total number of synapses. The total number of synapses is equal to the total number of neurons times the number of synapses per neuron, or $N\delta$. Thus, $L_{\text{intra}} \sim (N\delta/A)^{1/3}$. We have seen earlier that $\delta \sim W$ (because of the invariant area-infiltration constraint), and along with the α power law relationship $A \sim W^{\alpha}$, we can conclude that $\delta \sim A^{1/\alpha}$. We have also seen earlier that $A \sim N^{\alpha/(1+\alpha)}$, and we may derive that $L_{\text{intra}} \sim N^{2/[3(1+\alpha)]}$. We treat the average length of a white matter axon, L_{white}, as the linear dimensions of the brain, the latter whose volume scales approximately proportionally to gray matter volume (Changizi, 2001b), and so $L_{\text{white}} \approx V_{\text{gray}}{}^{1/3}$. Similar to the way we derived the relationship for L_{intra}, we get the relationship $L_{\text{white}} \sim N^{(2+\alpha)/[3(1+\alpha)]}$. p0120

We are now in a position to write the total wire volume, $V_{\text{totalWire}}$, as a function of N and the parameter α. $V_{\text{total Wire}} = V_{\text{intraWire}} + V_{\text{whiteWire}} = (N_{\text{intra}})(L_{\text{intra}})(R_{\text{intra}})^2 + (N_{\text{white}})(L_{\text{white}})(R_{\text{white}})^2$, and plugging the values derived above, we have p0125

$$V_{\text{totalWire}} \sim (N - N^{2\alpha/(1+\alpha)})(N^{2/[3(1+\alpha)]})(N^{1/[3(1+\alpha)]})^2 + (N^{2\alpha/(1+\alpha)})(N^{(2+\alpha)/[3(1+\alpha)]})(N^{1/[3(1+\alpha)]})^2$$

With some algebraic manipulation, this becomes

$$V_{\mathrm{totalWire}} \sim (N^{(4/3)/(1+\alpha)})[N + N^{(7/3)\alpha/(1+\alpha)} - N^{2\alpha/(1+\alpha)}]$$

p0130 Across the range of values for α (i.e., from 0 to 1) I numerically computed the scaling exponent of $V_{\mathrm{total\ Wire}}$ as a function of N (Figure 7). The exponent is minimal – and the total wire volume scales up most slowly – when $\alpha = 0.76$. In particular, when $\alpha = 0.76$, the $V_{\mathrm{totalWire}} \sim N^{1.7748}$. In contrast, for $\alpha = 0$ – the case where the number of areas remains constant with network size – $V_{\mathrm{totalWire}} \sim N^{2.33}$. On the other hand, when $\alpha = 1$ – corresponding to the fastest that the number of areas can scale up – $V_{\mathrm{total\ Wire}} \sim N^{1.833}$, which is not much faster than the optimal scaling at $\alpha = 0.76$. Accordingly, the predictions made by the economical well-connectedness hypothesis are very similar if we use $\alpha = 1$ instead of $\alpha = 0.76$.

p0135 Table 1 shows the approximate empirical scaling exponents for the variety of neocortical quantities discussed in Section 3.13.2 (both as a function of the number of neurons, and as a function of gray matter volume), along with the predictions of the above 'economical well-connectedness' model, and one can see close agreement, whether one uses the predicted exponent for the optimal $\alpha = 0.76$, or one uses the $\alpha = 1$ approximation.

s0070 3.13.5 Conclusion

p0140 Here we have summarized a variety of changes the neocortex undergoes in the transition from small to large brains (Section 3.12.2), pointed out two fundamental connectivity invariances (Section 3.12.3), and showed that the economical satisfaction of these invariances is central to an explanation of the many scaling features (Section 3.12.4). More specifically, mammalian neocortices appear to conform to two principles of connectivity, referred to as invariant well-connectedness. The first is invariant area-infiltration, which is the observation that the average number of synapses per neuron scales approximately proportionally with the average number of neurons per area. There appears to be, then, strong selective pressure across mammalian neocortices for the average number of synapses per neuron to scale up just fast enough that neuron-interconnectedness 'within areas' can remain invariant, 'and' that when an area connects to another area, the average neuron making the connection has a sufficient number of synapses to infiltrate an invariant fraction of the neurons in the area. The second principle of connectivity is invariant area-interconnectedness, which is the observation that the average number of area-connections per area scales approximately proportionally with the total number of areas. There appears, then, to be strong selective pressure across mammalian neocortices for the number of area-connections per area to scale up just fast enough that area-networks can maintain an invariant level of area-interconnectedness. Equivalently, there is selective pressure for the total number of area-area connections to scale as the square of the total number of areas. These two principles of invariant well-connectedness – and the two hierarchical tiers of invariant interconnectedness – appear to be central to the organization of the mammalian neocortex, and the 'economical' satisfaction of these invariances leads to the average number of neurons per area scaling approximately proportionally to the total number of areas. Since the total number of neocortical neurons is just the product of the number of neurons per area and the number of areas, it follows that the latter quantities scale as the square root of the total number of neocortical neurons. Because of invariant area-infiltration, it follows that the average number of synapses per neuron must also scale up as the square root of the total number of neocortical neurons, and a consequence of 'this' is that neuron density decreases and axon caliber increases as discussed in Section 3.12.2 (and these, in turn, were key to understanding why surface area and white matter volume scale the way they do).

p0145 We see, then, that these scaling relationships are primarily due to selective pressure for economically satisfying invariant well-connectedness, and are thus 'epiphenomenal', that is, are *not* signs of more complex computations *per se*. Left unanswered is what exactly is so important about conforming to invariant well-connectedness. There is clearly a theoretical elegance to the principle, but I have no *a priori* theoretical reason for why it should be selected for, nor why there are two tiers rather than, say, three.

p0150 Also left unanswered is why brain size increases with body size, namely approximately as the 3/4 power of body mass. Given the contemporary proclivity for treating the brain as a biological computer, it is mysterious why a larger, but not more behaviorally complex, mammal should require a larger brain at all, much less one that scales so considerably with body size. If brain size did not vary with body size, these scaling problems would, of course, vanish. We are currently in the embarrassing situation of understanding why neocortical features vary with brain size as they do, but not understanding why brains vary in size so much in the first place.

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