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Parcellation and Area-Area Connectivity as a Function of Neocortex Size

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Key Words
Neocortex · Scaling · Area · Connectivity · Comparative · Mammal

Abstract
Via the accumulation of data from across the neuroanatomy literature, we estimate the manner in which (i) the number of neocortical areas varies with neocortex size, and (ii) the number of area-area connections varies with neocortex size. Concerning parcellation, we find that the number of areas scales approximately as the 1/3 power of gray matter volume, or, equivalently, as the square root of the total number of neocortical neurons. A consequence of this is that the average number of neurons per area also scales approximately as the square root of the total number of areas. Concerning area-area connectivity, we find evidence that the total number of area-area connections scales as the square of the number of areas. These scaling results help constrain theories about the principles underlying neocortical organization.

Introduction

A central feature of the mammalian neocortex – noticed ever since Brodmann [Garey, 1999] – is that it is parcellated into multiple areas. Although it is well known that distinct areas have distinct functions, it is not understood why the neocortex has as many areas as it does. For example, is neocortical parcellation due to functional reasons, where having more areas implies a functionally more complex brain? Or, might neocortical parcellation be due to more epiphenomenal reasons, such as that bigger (but not necessarily more complex) brains must have more areas in order to keep volume costs or temporal delay costs down [Kaas, 1977, 1989, 1995, 1997, 2000; Braitenberg, 1978, 2001; Cowey, 1979, 1981; Barlow, 1986; Durbin and Mitchison, 1990; Mitchison, 1991, 1992; Ringo, 1991; Jacobs and Jordan, 1992; Ringo et al., 1994; Changizi, 2001, 2003b, 2005a, b]. In the hope of illuminating why the neocortex is parcellated, we measured how parcellation varies as a function of brain size, and also how area-area connectivity varies with brain size.

Materials and Methods

Brain mass information is used throughout the paper, and these data are averages from animals measured in Hrdlicka [1907], Von Bonin [1937], Crile and Quiring [1940], Stephan et al. [1981], the Stephan Collection, Hofman [1982] and Haug [1987]. 'Encephalization quotient' (EQ) is used in table 1, and in the text, and is computed as brain mass (grams) divided by the 3/4 power of body mass (grams). (That is, EQ is brain mass properly normalized by body mass.) Body masses are taken from the brain citations mentioned just above, and also from Nowak [1999]. We note that gray matter volume scales approximately proportionally with brain volume [Changizi, 2001], and so brain volume can be used as a proxy for gray matter volume.

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Table 1. Data for the average relative size of cortical areas for a number of animals, measured from flattened cortical maps

Animal	Latin name	Areas shown	Average rel. size, %	SD, log rel. size	Brain mass, g	EQ	Reference
Shrew	*Sorex, Blarina, Cryptotis*	4	7.434	0.226	0.218	0.04880	Catania et al., 1999
Mouse	*Mus musculus*	9	5.556		0.487	0.05686	Krubitzer and Huffman, 2000
Star-mole	*Condylura cristata*	3	4.692	0.697	1.077	0.06842	Krubitzer, 1995
Ghost bat	*Macroderma gigas*	4	5.493	0.395	1.704	0.04707	Krubitzer, 1995
Rat	*Rattus rattus*	10	5.000		1.778	0.03245	Northcutt and Kaas, 1995
Tenrec	*Echinops telfairi*	6	5.103	0.172	2.538	0.02202	Krubitzer et al., 1997
Tree shrew	*Tupaia belangeri*	8	5.927	0.298	3.114	0.06835	Lyon et al., 1998
Hedgehog	*Atelerix albiventris*	7	8.383	0.152	3.273	0.02246	Krubitzer et al., 1995
Quoll	*Dasyurus hallucatus*	8	5.322	0.368	4.666	0.05372	Krubitzer, 1995
Opossum	*Didelphis marsupialis*	8	5.549	0.234	5.174	0.01849	Beck et al., 1996
Ferret	*Mustela putorius*	11	4.545		5.226	0.08753	Manger et al., 2002
Squirrel	*Sciurus carolinensis*	15	2.889	0.336	6.522	0.08031	Krubitzer, 1995
Flying fox	*Pteropus poliocephalus*	11	3.333	0.358	7.223	0.05445	Krubitzer and Huffman, 2000
Marmoset	*Callithrix jacchus*	22	1.737	0.360	7.779	0.12740	Krubitzer, 1995
Platypus	*Ornithorhyncus anatinus*	6	6.153	0.548	9.000	0.03399	Krubitzer and Huffman, 2000
Echidna	*Tachyglossus aculeatus*	8	4.939	0.331	11.000	0.01850	Krubitzer, 1995
Owl monkey	*Aotus*	23	1.424	0.352	16.335	0.14591	Krubitzer and Huffman, 2000
Cat	*Felis domesticus*	22	2.273		27.093	0.07449	Kaas, 1987
Macaque	*Macaca*	25	0.987	0.467	84.643	0.21853	Krubitzer, 1995

Data are ordered here by brain size. The third column shows the number of areas indicated in the study. The fourth column is the average relative size of cortical areas in the study (10 to the power of the average logarithm of relative size), and the fifth column the standard deviation of the logarithms of relative size. Data are plotted in figure 1b. EQ = Encephalization quotient.

Methods for Parcellation

'Areas' are groups of neurons that communicate with one another largely via short-range, non-white-matter connections; whereas the connections between neurons in different areas are largely made by long-range, white-matter, connections. This definition of area is related to one of the three principal experimental criteria for identifying areas, namely the pattern of connectivity to other parts of the neocortex (the other two criteria concern histology and topographic maps). The definition is also similar to the notion of a 'partition' in computer electronics [Sherwani, 1995].

There are two difficulties in attempting to measure how the number of areas scales with brain size: (i) Different research groups do not always agree on a parcellation. We have sought to minimize this problem by confining ourselves to studies within one research group, namely that of Kaas, Krubitzer and colleagues. This group of researchers also has an advantage in that they have studied parcellation in a much greater variety of animals than any other group. (ii) The second difficulty is that few animals have been completely mapped by any research group; currently only macaque and cat have any claim to this. Related to this difficulty is that, even among the Kaas-Krubitzer parcellations, it is not the case that each animal has been studied to the same degree – greater attention to parcellation has been given to some animals over others. Measuring parcellation by simply counting the number of known areas for an animal within the Kaas-Krubitzer literature is therefore expected to have significant errors (although when one does this, parcellation scales almost the same as we find in this paper [Changizi, 2001]). We avoid the second difficulty here by switching from testing how par-

Table 2. Data for relative size (as a percentage of neocortex) of selected areas in a number of animals

	Relative size of area, %				
	V1	V2	A1	S1	M1
Shrew	5.445		4.230	12.651	
Mouse					
Star-nosed mole	0.962		4.502	23.837	
Ghost bat	3.833		9.402	13.815	
Tenrec	6.054		4.344	10.235	
Tree shrew	23.635	6.194	3.899	8.701	
Hedgehog	10.764	6.158	6.436	14.526	10.463
Quoll	21.095	6.708	2.957	11.449	5.845
Opossum	12.659	6.062	8.859		
Squirrel	19.680	4.486	1.584	8.081	4.573
Flying fox	14.636	5.133	1.026	8.198	6.050
Marmoset	15.375	6.468	0.678	4.029	4.772
Platypus	1.607		1.198	22.035	10.203
Echidna	8.331		1.401	7.557	13.534
Owl monkey	14.714	6.982	1.468	3.678	2.097
Macaque	17.699	9.463	0.468	1.664	1.897

Sources are those in table 1. Data are plotted in figure 2.

Table 3. Number of cortical areas and total number of area-area connections in a variety of neocortical sensory (or sensory-motor) subnetworks

Subnetwork	Areas	Edges	Reference
Tree shrew, visual	8	22	Lyon et al., 1998
Rat, visual	9	36	Coogan and Burkhalter, 1993
Macaque, auditory	13	56	Hackett et al., 1998
Macaque, auditory	16	95	Young, 1993
Macaque, somato-motor	17	100	Young, 1993
Macaque, auditory +	19	123	Kaas and Hackett, 2000
Cat, auditory +	20	153	Scannell and Young, 1993
Cat, visual +	26	264	Scannell and Young, 1993
Cat, somato-motor +	27	348	Scannell and Young, 1993
Macaque, visual	30	300	Young, 1993

+ indicates that there are other cortical areas included in the subnetwork. Data are plotted in figure 3a.

cellation scales as a function of brain size to instead testing how the average relative size of an area (i.e., the percentage of neocortex taken up by an area) scales. In a neocortex with more areas, the average relative size of an area must (as a matter of logic) decrease. For example, a neocortex with 20 areas has areas taking up, on average, 5% of the neocortex. Thus, from an estimate of the average relative size of areas within a neocortex, one can compute the extrapolated number of areas in the neocortex. For example, if one measures 10 areas in a neocortex and finds that the average relative size among them is 5%, then the extrapolated number of areas is 20.

Using papers published within the Kaas-Krubitzer literature, we scanned in figures of flattened parcellation maps, and used the NIH Image software to measure the surface area of each area with boundaries given in the figure. By also measuring the surface area of the entire neocortex in the figure, we could compute the relative size of each area in the figure. Table 1 shows average relative sizes from areas in a number of animals from the Kaas-Krubitzer literature, along with brain volumes and encephalization quotients (brain volume divided by the 3/4 power of body mass). For four animals – mouse, rat, ferret, and cat – only unflattened cortical maps were available, so measurements of relative size were not possible. In these cases, the number of areas was simply counted and assumed to in total fill the same overall amount of neocortex as that in the other studies (which averaged 50%; SD 12%), and the relative size computed as the inverse of twice the counted number of cortical areas. Standard deviations are accordingly not provided for these animals. Table 2 shows the relative sizes for some specific areas – namely, V1, V2, A1, S1 and M1 – across a number of mammals from the same literature. In some animals data do not exist for some areas.

Methods for Area-Area Connectivity

Areas are connected to other areas via white-matter axons. How does area-area connectivity vary with brain size? Measuring this is difficult for two reasons: (i) Attempts at building area-area connectivity matrices for the entire neocortex have been made only for macaque [Young, 1993] and cat [Scannell and Young, 1993; Scannell et al., 1995]. This means there are only two data points available. (ii) These two animals differ little in their number of areas (at least as found in the published connectivity matrices), and thus they provide effectively no range in network size with which to test the scaling prediction. We have circumvented these difficulties in two distinct ways.

First, in lieu of whole-brain area networks we have instead acquired data from neocortical subnetworks, as shown in table 3. In addition to circumventing the problems of number and range of data, this has the advantage that the connectivity matrix for a subnetwork is more likely to be fully understood. We have also confined our study to sensory (and somato-motor) subnetworks, for one might expect that the proportionality constants are more similar among sensory-motor subnetworks, whereas they may differ between sensory-motor and non-sensory-motor subnetworks (although the scaling exponents might be the same).

Second, although as mentioned above published connectivity matrices for whole brains are rare, there are a number of studies of the whole-brain connectivity patterns of specific areas of interest. We confined ourselves to sensory (and somato-motor) areas, and compiled estimates of the number of area-connections per area for areas and animals in table 4. For each animal, the average number of area-connections per area was computed, where averages were taken over the logarithms of values because in scaling studies this is appropriate (these are called 'log-transformed averages'). These averages are listed in table 5.

Results

Parcellation

Figure 1a shows the relative size of each measured area as a function of the size of the brain the area lies in, and one can see that (a) larger brains tend to have more areas measured by the Kaas-Krubitzer research groups (i.e., the number of dots per column in fig. 1a increases), and, more importantly, (b) the relative sizes tend to decrease with brain size, a sure sign that there are more areas. Figure 1b shows the average relative sizes of areas as a function of

Table 4. Number of area connections per area for a variety of areas from a variety of animals, with citations shown

Animal	Kind of areas	Area	Area connections per area	Reference
Opossum	visual	V1	5	Kahn et al., 2000
	somatosensory	S1	4	Beck et al., 1996
Owl monkey	visual	V1	11	Lyon and Kaas, 2002b
		DM	14	Beck and Kaas, 1998a
		VP	9	Beck and Kaas, 1998a
		MT	7	Krubitzer and Kaas, 1990a
Squirrel monkey	visual	V1	11	Lyon and Kaas, 2002b
		DM	15	Beck and Kaas, 1998a
		MT	7	Krubitzer and Kaas, 1990a
Marmoset	visual	V1	12	Lyon and Kaas, 2001
		V2	6	Lyon and Kaas, 2001
		MT	7	Krubitzer and Kaas, 1990a
	somatosensory	S1 (3b)	8	Krubitzer and Kaas, 1990b
		SII	12	Krubitzer and Kaas, 1990b
Bushbaby	visual	MT	7	Krubitzer and Kaas, 1990a
		V1	8	Lyon and Kaas, 2002a
		DM	12	Beck and Kaas, 1998b
		V2	10	Collins et al., 2001
Tree shrew	visual	V1	4	Lyon et al., 1998
		V2	7	Lyon et al., 1998
		TD	4	Lyon et al., 1998
		TA	4	Lyon et al., 1998
		TD	5	Lyon et al., 1998
		TP	5	Lyon et al., 1998
Rat	somatosensory	S1	7	Fabri and Burton, 1991
Flying fox	somatosensory	S1 (3b)	6	Krubitzer et al., 1993
		1/2	5	Krubitzer et al., 1993
		SII	8	Krubitzer et al., 1993
		PV	6	Krubitzer et al., 1993
		LP	10	Krubitzer et al., 1993
Squirrel	visual	V1	3	Kaas et al., 1989
		V2	10	Kaas et al., 1989
	somatosensory	S1 (3b)	5	Krubitzer et al., 1986; Krubitzer and Kaas, 1990b
		SII	6	Krubitzer et al., 1986; Krubitzer and Kaas, 1990b
		PV	8	Krubitzer et al., 1986
Cat	40 sensory areas	not shown here		Scannell et al., 1995
Macaque	8 visual areas	not shown here		Lewis and van Essen, 2000
	56 sensory-motor areas	not shown here		Young, 1993

The average number of area connections per area for each animal are shown in table 5, and plotted in figure 3b.

Table 5. Average number of area connections per area (10 to the power of the average base-10 logarithm of the number of area connections per areas), standard deviation of the logarithm of the number of area connections per area, and brain mass for a variety of animals (ordered by brain mass)

Animal	Latin name	Average area connections per area	SD log area connections per area	Brain mass g
Rat	*Rattus rattus*	7.00	0.00	1.78
Tree shrew	*Tupaia belangeri*	4.73	0.10	3.11
Bushbaby	*Galago senegalensis*	9.05	0.10	4.57
Opossum	*Didelphis marsupialis*	4.47	0.07	5.17
Squirrel	*Sciurus carolinensis*	5.91	0.20	6.52
Flying fox	*Pteropus poliocephalus*	6.79	0.12	7.22
Marmoset	*Callithrix jacchus*	8.65	0.14	7.78
Owl monkey	*Aotus*	9.92	0.13	16.34
Squirrel monkey	*Saimiri sciureus*	10.49	0.17	22.48
Cat	*Felis domesticus*	13.34	0.24	27.09
Macaque	*Macaca*	16.99	0.32	84.64

See methods for references and cortical areas. Data are plotted in figure 3b.

brain size (data directly from table 1). Figure 1c shows the extrapolated number of cortical areas in the entire animal's neocortex, A, versus brain volume (from table 1), and the best-fit exponent is 0.3067 (95% confidence interval is 0.159, 0.455). Gray matter volume, V_{gray}, scales approximately proportionally with brain volume (see Methods), and thus it is approximately the case that $A \sim V_{gray}^{1/3}$. Because the number of neocortical neurons, N, scales approximately as the 2/3 power of gray matter volume [Tower and Elliott, 1952; Tower, 1954; Jerison, 1973; Passingham, 1973; Prothero, 1997b], it follows that $A \sim N^{1/2}$. Finally, because $N = A \times W$, where W is the average number of neurons per area, it follows that approximately $W \sim A$, and so $W \sim V_{gray}^{2/3} \sim N^{1/2}$.

Figure 1b shows that the average relative size of an area decreases in larger neocortices, but in figure 1a one can observe that there are always some areas that remain large, namely above a relative size of about 10%. Which areas might these be? We examined the scaling of five particular areas: V1, V2, A1, S1 and M1 (see table 2). Figure 2 shows how the relative sizes of these areas scale as a function of brain size. Among this group of mammals, V1 and V2 do not scale down [best-fit exponent for V1 is 0.291 with 95% confidence interval (–0.096, 0.678), and for V2 is 0.138 with 95% confidence interval (0.0246, 0.2506)]. Instead, they fill a nearly invariant fraction of neocortex – the numbers of neurons in each of V1 and V2 appear to scale approximately proportionally to the total number of neocortical neurons, or $W_{V1} \sim W_{V2} \sim N$ (as opposed to the average number of neurons per area, $W \sim N^{1/2}$). The distinctive scaling of V1 and V2 among our group of mammals is not explained by their being early sensory areas, for A1 and S1 scale down like most areas (as does M1). This characteristic of V1 and V2 does not appear to be common among areas: among the 25 areas measured in macaque, it appears that only V1 and V2 show this, as can be seen by examination of the rightmost vertical array of points for macaque in figure 1a, where there are just two unusually large areas at the top right, and they are V1 and V2. These results might have a connection to Steven's [2001] idea that V1 encodes one more dimension than LGN, and thus the number of neurons in V1 scales as the 3/2 power of that for LGN. We note that V1 and V2 appear to slightly increase [e.g., see Snow et al., 1997; Kingsbury and Finlay, 2001], but for our data this is primarily due to the fact that the larger brained animals in our data are primates, with enlarged visual cortices; deletion of Macaque, for example, removes the correlations. Among primates Frahm et al. [1984] find that the relative size of V1 decreases with brain size. However, Rosa et al. [1993] find roughly an invariant relative size for V1 in primates and non-primates: their figure 3 shows that V1 surface area scales as body mass to approximately the 2/3 power. Because gray matter volume scales approximately as body mass to the 3/4 power [Allman, 1999], V1 surface area scales as gray matter volume to the 8/9, which is the same scaling exponent as the entire cortical surface area [see references within Changizi, 2001].

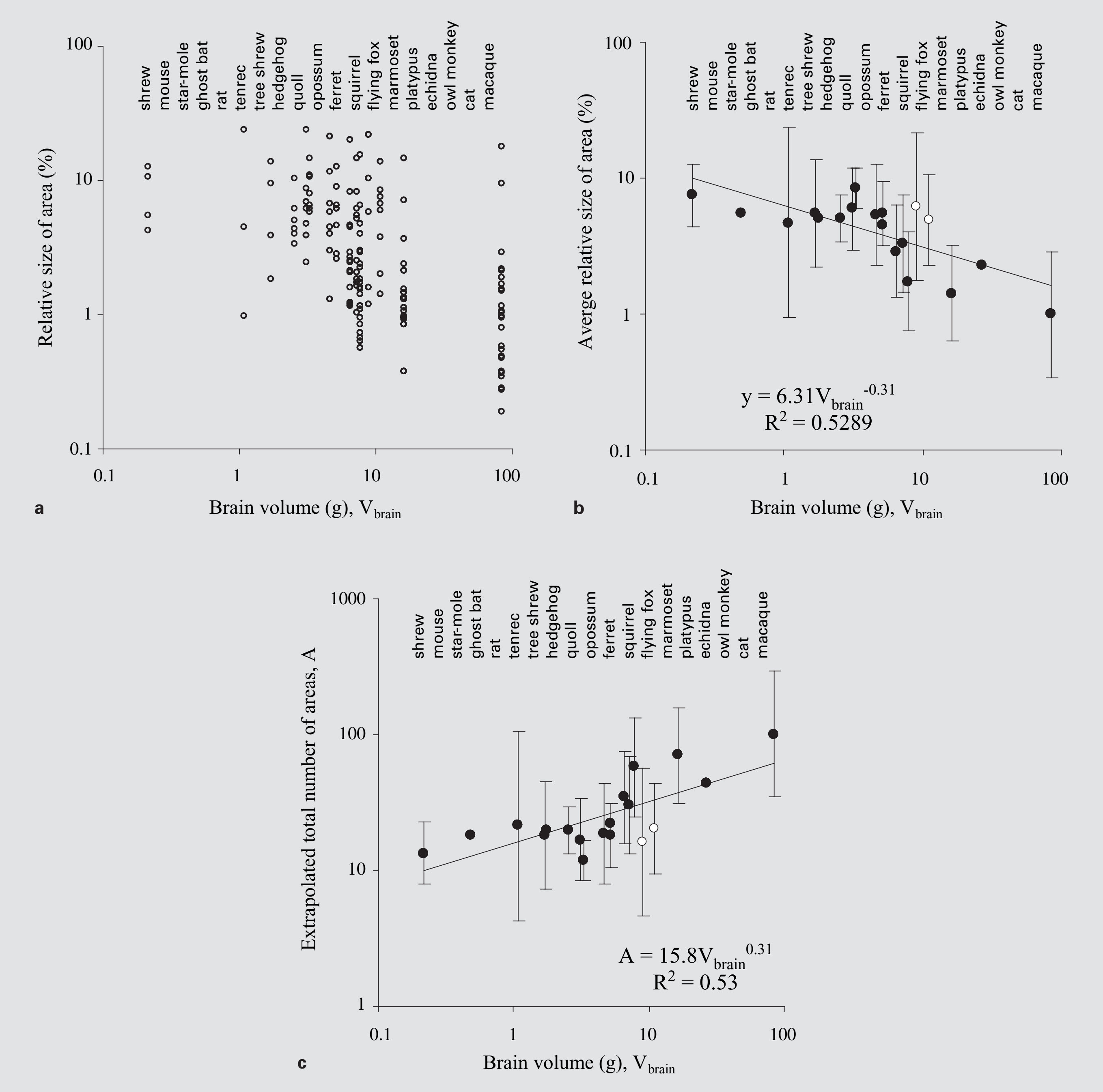

Fig. 1. Scaling of parcellation. **a** Log-log (base 10) plot of the relative size of cortical areas (as a percentage of neocortex) versus brain mass (grams) for sensory (and somato-motor) areas. Data are from table 1. One can see that larger brains have more known areas, and they tend to fill a smaller fraction of neocortex. **b** Log-log (base 10) plot of the (log-transformed) average relative size versus brain mass (grams), for data in table 1. Error bars show standard deviations. White circles are monotremes, and if one excludes them the best-fit exponent is –0.338, with correlation rising to $R^2 = 0.64$. **c** Log-log (base 10) plot of the extrapolated total number of areas versus brain mass (g).

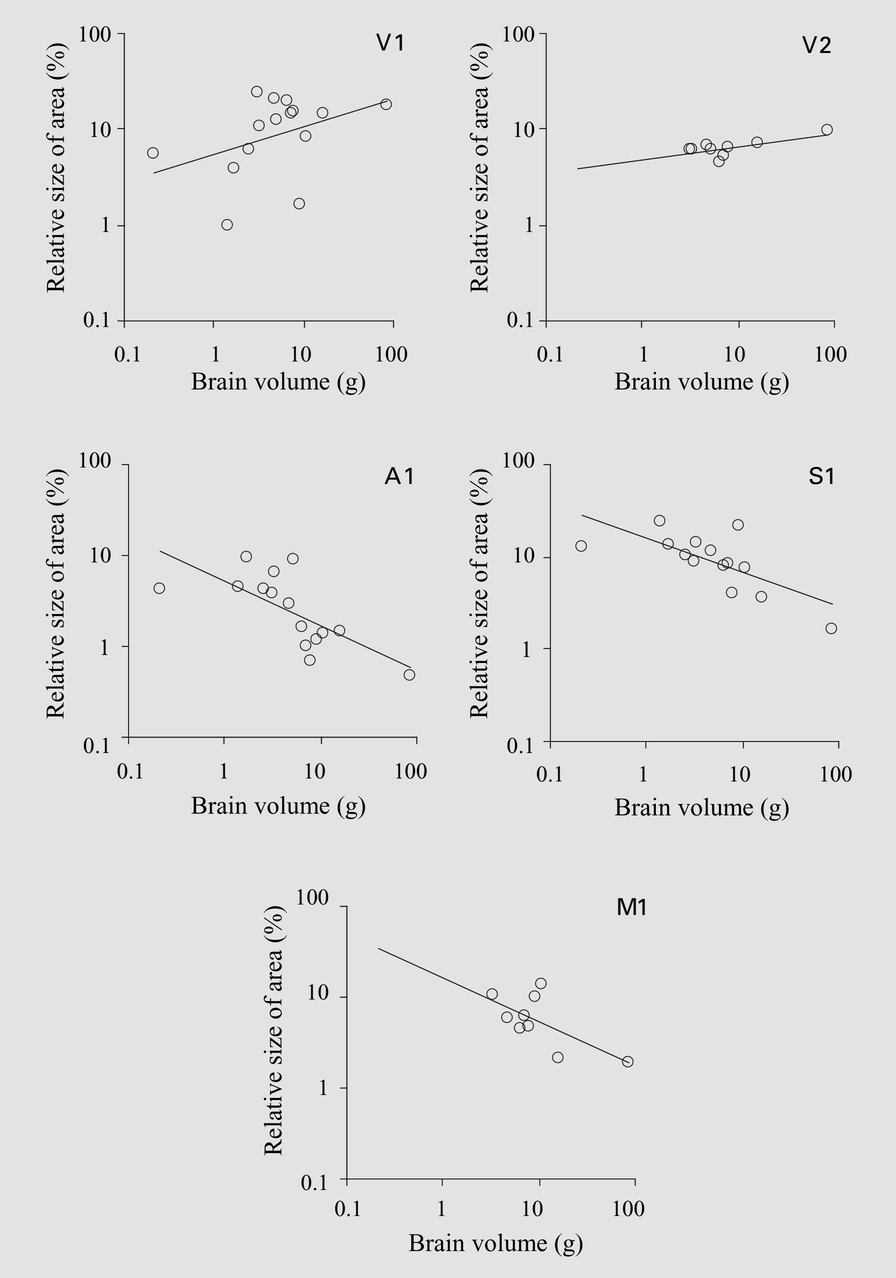

Fig. 2. Log-log (base 10) plot of the relative size of a cortical area (as a percentage of neocortex) versus brain mass (grams), for five cortical areas. Data are from table 2. Figure 1a shows that most areas decrease in relative size as a function of brain size, and one can see here that A1, S1 and M1 scale like the 'typical' area. V1 and V2 do not scale down, however.

Area-Area Connectivity

We first report how the total number of area-area connections, G, varies as a function of the number of areas, A, across subnetworks in tree shrew, rat, cat and macaque (see table 3). Figure 3a shows these data and the best-fit exponent is 2.035 (95% confidence interval is 1.807, 2.263). Therefore, it is approximately the case that $G \sim A^2$, and this means the number of area-area connections scales up (across subnetworks of varying size) as quickly as possible. Because $G = A \times D$, where D is the average number of area-connections per area, it follows that $D \sim A$. Also, using our earlier empirical conclusion concerning how the number of areas scales, we can conclude that $D \sim V_{gray}^{2/3} \sim N^{1/2}$ (assuming that these subnetwork scaling results are indicative of scaling across brains). The best-fit power law equation for the number of area-area connections versus the number of areas in subnetworks (fig. 3a) is $G \approx (1/3)A^2$, and this proportionality constant

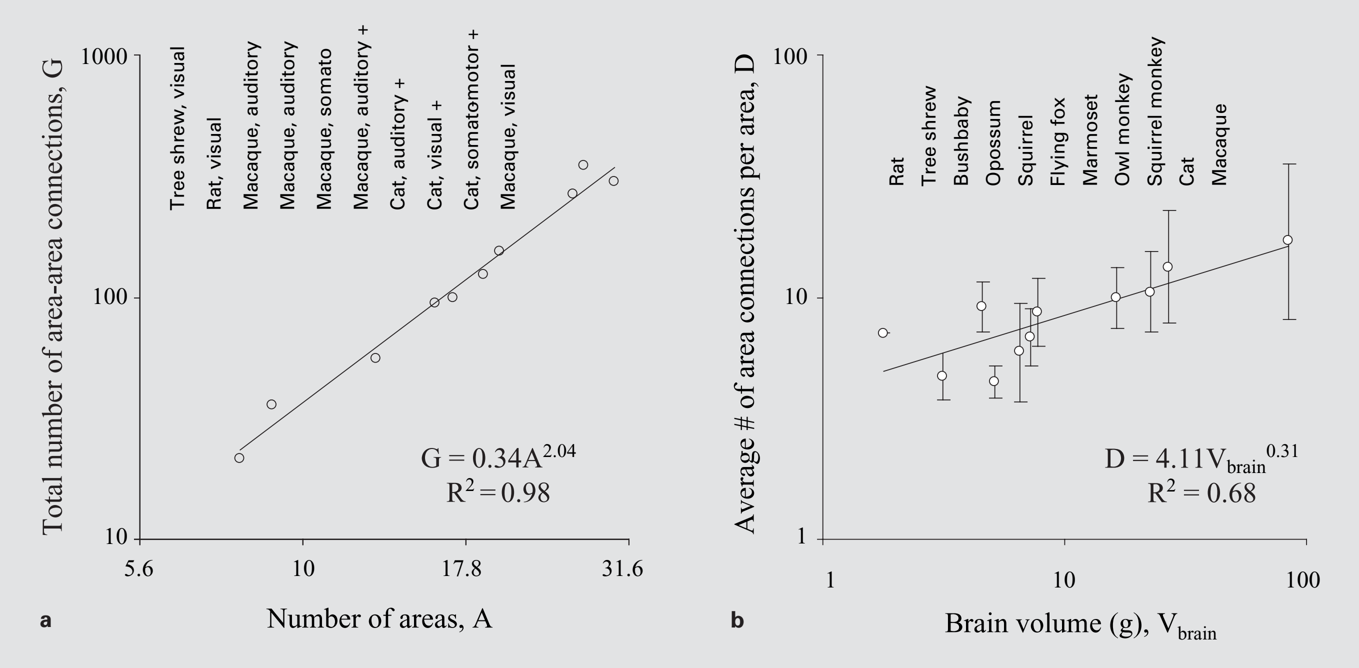

Fig. 3. Scaling of area-area connectivity. **a** Log-log (base 10) plot of the total number of (known) area-area connections G versus the number of areas A, in sensory (and somato-motor) subnetworks. Data are from table 3. Best-fit line via linear regression is shown (as is true in all the figures here), and is approximately $G \sim A^2$. In fact, paying attention to the intercept gives us $G \approx (1/3)A^2$, which shows that roughly 1/3 of the total possible number of connections exist independent of network size. **b** Log-log (base 10) plot of the average number of area connections per area (the number of areas with which an area connects) D versus brain volume, for sensory (and somato-motor) areas. Error bars show standard deviation. Data are from table 5 (and table 4). If one keeps only the data from table 4 from Kaas, Krubitzer and colleagues (i.e., if one confines to what is more probably a single research methodology), the number of data points drops from 11 to 8, the x-axis range drops nearly in half, the correlation drops to $R^2 = 0.55$, and the best-fit exponent becomes 0.38.

means that roughly 1/3 of all the possible connections exist in these subnetworks. This is an underestimate, given that researchers are still discovering new connections. However, it is may be an overestimate for the percentage of possible connections existing for the entire neocortex, because the subnetworks consist of functionally related areas which might be more closely interconnected than is the entire neocortex.

The empirical result above concerning area-area connectivity considered scaling across subnetworks, not scaling across different mammalian brains. Figure 3b shows the average number of area-connections per area, D, for the 12 mammals (from table 5) as a function of brain volume, and the best-fit exponent is 0.31 (95% confidence interval is 0.145, 0.468). That is, we come to the same conclusion as we did from the subnetwork plot above: it is approximately the case that $D \sim {V_{gray}}^{1/3} \sim N^{1/2}$.

Discussion

We have found evidence that both the number of neocortical areas and the average number of area-connections per area scale approximately as the 1/3 power of gray matter volume, or as the square root of the total number of neocortical neurons. Alternatively, these values scale as the 3/8 power of the total neocortical surface area because surface area is known to scale approximately as the 8/9 power of gray matter volume [Jerison, 1982; Prothero and Sundsten, 1984; Hofman, 1985, 1989, 1991; Prothero, 1997a]. If we extrapolate these power laws to brains of human size (≈ 1,300 g), we expect approximately 60 area connections per area, 150 areas, and 9,000 area-area connections in all. Extrapolating to brains the size of an elephant (≈ 5,000 g), we expect approximately 90 area connections per area, 220 areas, and 21,000 area-area connections in all. We caution, however, that the data are still fragmentary: (i) the areas and animals included in the study have not been chosen at random, but rather are the ones that have been of interest to researchers, (ii) some of the variation may well reflect behavioral specializations, not brain size per se, and (iii) 'lower' sensory areas are over-represented compared to 'higher' areas.

From the scaling relationships measured here, along with previously known relationships, we can identify three surprising and fundamental invariants. The first is that the total number of areas scales approximately proportionally to the average number of neurons per area – i.e., $A \sim W$ – which entails that each scales as the square root of the total number of neocortical neurons. This may be called the 'square root compartment invariance', a version which was first conjectured by Braitenberg [1978, 2001] and Braitenberg and Schuz [1998]. The second is that the average number of area connections per area scales approximately proportionally to the total number of areas, i.e., $D \sim A$. This may be called 'invariant area-interconnectedness,' a version which was also suggested first by Braitenberg [1978, 2001; see also Changizi, 2001]. The third and last fundamental invariant is that the average number of synapses per neuron, δ, scales approximately proportionally to the average number of neurons per area, W; i.e., $\delta \sim W$. This may be called 'invariant area-infiltration,' and was first suggested in Changizi [2001]. (The combination of the second and third invariants are called 'invariant well-connectedness.') Unlike the first two invariants, which followed directly from results of this paper, invariant area infiltration relies on a measurement of how the average number of synapses per neuron, δ, scales, and this is not something we measured here. However, from previously known scaling relationships we can compute how δ scales with brain size. We mentioned earlier that the total number of neocortical neurons, N, scales disproportionately slowly as a function of gray matter volume, and specifically, $N \sim V_{gray}^{2/3}$. The volumetric density of synapses in neocortex, however, appears to not vary as a function of brain size [Abeles, 1991; Changizi, 2001], and therefore the total number of synapses in the gray matter scales directly proportionally to gray matter volume. It follows from these two scaling relationships that the average number of synapses per neuron, δ, must scale as the 1/3 power of gray matter volume; i.e., $\delta \sim V_{gray}^{1/3}$, or, equivalently, $\delta \sim N^{1/2}$. But recall that we found that the average number of neurons per area, W, also scales in approximately this manner, and therefore $\delta \sim W$. In total, these three invariants can be summarized by $D \sim A \sim W \sim \delta \sim N^{1/2}$.

The satisfaction of these three invariants is central to understanding how many of the other neocortical features scale with brain size. For example, increasing the average number of synapses per neuron means that neuron density must decrease in larger brains, as it in fact does; and this is crucial in explaining why neocortical gray matter surface area and thickness scale up as they do, which concerns why the neocortex becomes increasingly convoluted [Changizi, 2001]. The increasing average number of synapse per neuron also requires that neurons have larger somas and axon calibers to support the greater number of 'leaves' [Cherniak et al., 1999; Changizi, 2001; Shultz and Wang, 2001; Harrison et al., 2002], and this is key to explaining why white matter volume increases disproportionately quickly compared to gray matter volume [Changizi, 2001, 2003b].

Why do these three invariants hold across mammalian neocortices? Invariant area infiltration – i.e., the constraint that the average number of synapses per neuron scales proportionally to the average number of neurons per area – may be due to selective pressure for some minimum threshold of neuron interconnectedness within areas, and a selective pressure for inter-area neurons to infiltrate some minimum fraction of the neurons in the area to which it connects. Similarly, invariant area interconnectedness – i.e., the constraint that the average number of area connections per area scales proportionally to the total number of areas – may be due to selective pressure for some minimum threshold of connectivity at the area-area level. Together, these two connectivity invariances comprise 'invariant well-connectedness,' and amount to a two-tiered hierarchical approach to neocortex design, where each tier possesses invariant interconnectedness, but where there is not invariant interconnectedness at the level of the entire neocortex. We do not have any explanation for why there is selection pressure for such a two-tiered approach (why not three tiers?). The square root compartment invariance – i.e., the constraint that the average number of neurons per area scales proportionally to the total number of areas – can be explained by a hypothesis that, given that invariant well-connectedness must (for whatever reason) be satisfied across neocortices of varying size, the most economical way of satisfying invariant well-connectedness is to scale the number of areas proportionally to the average number of neurons per area. This is called 'economical well-connectedness' [Changizi, 2001, 2003b, 2005; Changizi and He, 2005].

Note that brain size among mammals is not a correlate of behavioral complexity – average mammalian behavioral repertoire sizes from eight mammalian orders

[Changizi, 2003a] do not correlate with brain size ($R^2 = 0.1$, d.f. = 6, t = 0.816, $p > 0.2$) – and thus the area increases we see in figure 1c are due to increasing brain size, not to increasing functional complexity [see also Aboitiz, 1996]. The variation in figure 1c leaves enough room, however, for there to be some truth behind the general feeling that functionally more complex animals have more areas. But how are we to measure the 'functional complexity' of an animal in order to test this? It has long been noted that encephalization quotient, EQ (the residual on a log-log brain-versus-body-mass plot) correlates well with our intuitive judgment of the intelligence of an animal, and Changizi [2003a] showed that behavioral repertoire size (as measured by ethologists) indeed correlates highly with EQ among mammals (for 8 mammalian orders, the correlation is $R^2 = 0.84$, d.f. = 6, t = 5.61, $p < 0.001$). Table 1 possesses data for EQ, and a plot of average relative sizes of areas versus EQ (not shown) shows that greater EQ tends to imply lower average relative sizes of areas, and thus a greater extrapolated total number of areas ($A \sim EQ^{0.65}$, $R^2 = 0.61$). (Note that the extrapolated total number of areas divided by $EQ^{0.65}$ – i.e., the number of areas 'corrected' by EQ – correlates significantly with brain size: $R^2 = 0.44$.) This thereby provides support for the feeling that 'smarter' animals have more areas: functionally more complex animals have more areas compared to the base-line expectation for their brain size. But we cannot expect there to be an isomorphic map between functional specializations and cortical areas: large network size may require parcelling one function into more than one area, and small networks may require lumping multiple functions into one area [e.g., Kaas, 1987].

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