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Brain Size and Number of Neurons: An Exercise in Synthetic Neuroanatomy

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Abstract. Certain remarkable invariances have long been known in comparative neuroanatomy, such as the proportionality between neuronal density and the inverse of the cubic root of brain volume or that between the square root of brain weight and the cubic root of body weight. Very likely these quantitative relations reflect some general principles of the architecture of neuronal networks. Under the assumption that most of brain volume is due to fibers, we propose four abstract models: I, constant fiber length per neuron; II, fiber length proportionate to brain diameter; III, complete set of connections between all neurons; IV, complete set of connections between compartments each containing the square root of the total number of neurons. Model I conforms well to the cerebellar cortex. Model II yields the observed comparative invariances between number of neurons and brain size. Model III is totally unrealistic, while Model IV is compatible with the volume of the hemispheric white substance in different mammalian species.

Keywords: comparative neuroanatomy, allometric relations, brain volume

1. Introduction

Brains of different animals have much in common. For one thing, they are essentially composed of neurons, cells specialized in producing long filiform appendages that mediate the connections between them (and make up most of the volume of the brain). All mammalian brains are of comparable size, if we take relative measures and allow for dependances other than simple proportionality between body and brain weight. In fact, animals of different sizes have brain weights roughly proportionate to the surface, not to the volume of their bodies (Jerison, 1973). Some more invariants or quasi-invariants that hold across a variety of animal species were discovered by comparative neuroanatomists. The density of neurons in the nerve tissue of different species decreases with the size of the brain (and of the animal), being inversely proportionate to the cubic root of the volume of the brain (Shariff, 1953; Tower, 1954; Bok, 1959). Correspondingly, the length of the processes emanating from one neuron increases with the cubic root of brain size (Bok, 1959).

These quantitative relationships invite speculation. In some cases an explanation is at hand, as for the two-thirds-power law relating brain size and body size: it is mostly surfaces that mediate the contacts between the animal and the world and therefore command the brain's attention (Jerison, 1973). In other cases the explanations are not so straightforward. Why should a larger version of a smaller brain have a cell density as if it was stretched in one direction only (that is, inversely proportionate to one of its diameters) rather than inversely proportionate to its volume, as you would expect if it were simply blown up proportionately in every direction? Worse still, why should the density of neurons be inversely proportionate to the cubic root of the surface of the animal's body (that is, to the cubic root of brain volume), which is, all told, the minus 2/9 power of the animal's weight?

Not every quantitative relationship lends itself to a reasonable interpretation, and we must select the right ones. We may take hints from idealized situations that we construct out of very schematic neurons, deliberately ignoring factors known to affect various measures in the brain, such as the amount of glia and other non-neural tissue elements, as well as the obvious variations in the fine structure of neurons and in the pattern of their connections. We shall assume that the entire volume of the brain is given by the sum of the volumes of the fibers (cell processes, including dendrites and axons), with a negligible contribution from the neural cell bodies. We also shall assume that all fibers have the same thickness.

2. Four Models

I. *Brains of Different Sizes Composed of Standard Neurons of Uniform Size*

This is the simplest case, so simple that it would hardly seem to correspond to anything in nature. However, it does have at least one application, as we shall see.

If N is the number of neurons in a brain, and f (μm) is the sum of the lengths of all dendrites and axons belonging to each neuron, the volume of the brain will be simply $V = Naf$ (in cubic μm). The constant a represents the (average) cross-sectional area of cell process, which for convenience we put equal to 1 (one square micron would be a reasonable assumption for real brains). The density $D = N/V$ of neurons in the tissue is $1/af$, the same for brains of all sizes.

II. *Length of Cell Processes Proportionate to the Diameter of the Brain*

It may be reasonably assumed that neurons communicate with each other over a distance that varies with the size of the brain. Let us assume for simplicity that f is equal to d, the linear dimension of a brain that we imagine to have the shape of a cube.

We have then

$$V = Nfa = NV^{1/3} \text{ (since } f^3 = d^3 = V, \text{ and } a = 1)$$
$$N = V^{2/3}$$
$$V = N^{3/2}.$$

The neural density turns out to be

$$D = N/V = N/N^{3/2} = 1/N^{1/2}$$

—that is, inversely proportionate to the square root of the number of neurons.

The density as a function of brain volume is

$$D = N/V = V^{2/3}/V = 1/V^{1/3}$$

—that is, inversely proportionate to the cubic root of the volume.

III. *Complete Set of Connections Between Neurons*

If every neuron were connected to each of the other neurons in the brain, the number of the connecting fibers would be $N^2 - N$ (which we may take as N^2 for large N), and their length would vary according to the relative position of the neurons, from $f =$ very small, to $f = d$. Taking $r = 0.5d$ as an approximation to their average length (for a sphere with radius r, Perelmouter, 2000, calculates an average length of $1.067r$), we get a volume

$$V = raN^2$$

and, since $d = 2r = V^{1/3}$, and $a = 1$,

$$2V/V^{1/3} = 2V^{2/3} = N^2$$
$$N = 2^{1/2}\, V^{1/3}$$
$$V = 2^{-3/2}\, N^3.$$

In this case, the neural density

$$D = N/V = N/2^{-3/2}N^3 = 2^{3/2}N^{-2}$$

varies inversely with the square of the number of neurons, or, as a function of volume:

$$D = N/V = 2^{1/2}\, V^{1/3}/V = 2^{1/2}\, V^{-2/3}.$$

IV. *Fully Connected Square Root Compartments*

If the problem is to connect every part of the brain with every other part without incurring in impossibly large numbers of connections (and, therefore, impossibly large volumes), a reasonable strategy would be to subdivide the brain into compartments and allow for a complete set of connections between compartments. A realistic scheme for a brain containing N neurons would be a parcellation into $n = N^{1/2}$ compartments each containing $n = N^{1/2}$ neurons, so that the neurons of a compartment can each send one fiber to one of the other compartments (Braitenberg, 1978). Disregarding the connections between neurons within a compartment, one would then obtain $n^2 = N$ connections, again of length $r = 1/2d = 0.5V^{1/3}$ and a volume

$$V = 1/2\, NV^{1/3}a \quad (a = 1)$$
$$V/V^{1/3} = V^{2/3} = 1/2N$$
$$V = (1/2N)^{3/2} = 0.35N^{3/2}$$

—that is, proportionate to the cube of the square root of N, as in case II above.

The neural density is then

$$D = N/V = 0.5^{-3/2}N^{-1/2}$$

inversely proportionate to the square root of N, again as in case II, or, as a function of volume

$$D = N/V = 2\ V^{-1/3}.$$

3. Real Brains

Unashamedly unrealistic as our schemes I to IV may seem, they do yield some values that are remarkably close to measurements on real brains.

Case I predicts a uniform density of tissue elements in brains of different sizes. This is not the case for the brain as a whole but may hold for some parts of the brain that, as brains get bigger in evolution, simply grow by apposition of new tissue without essential changes in the already existing structure. This could be expected in a nerve net with only local interactions whose range does not depend on the size of the whole structure and therefore on the size of the animal. The cerebellar cortex comes close to this. Most of its volume is provided by the so-called parallel fibers, which run in a laterolateral direction as the T-shaped branches of the axons of granular cells, by far the most numerous cell type in the cerebellum (and, in higher vertebrates, in the whole brain as well). The length of the individual parallel fiber is remarkably constant (a few millimeters in each direction) in brains of different sizes (Mugnaini, 1983; Harvey and Napper, 1988), spanning the whole width of the cerebellum in the smallest specimens and a fraction of its lateral extension in the bigger ones (Braitenberg, 1977). Also, their thickness does not seem to vary much, so that the contribution of the individual granular cell to the cerebellar volume is roughly constant.

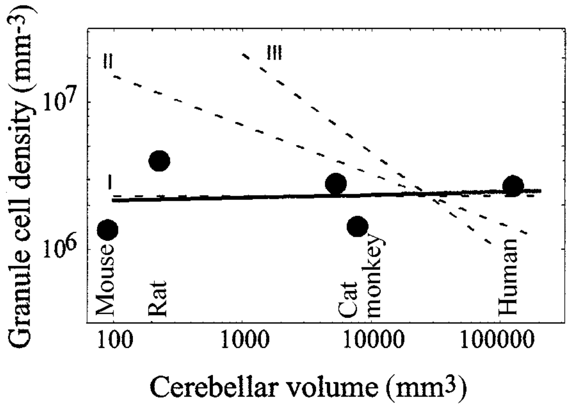

Figure 1. Granular cell density in the granular cell layer of the cerebellar cortex as a function of the volume of the entire cerebellum, plotted on log-log coordinates for five mammalian species. The solid line is the regression line; the three dotted lines indicate the expected dependences for our schemes I, II, and III. Data from Andersen et al. (1992), Caddy and Biscoe (1979), Korbo and Andersen (1995), Korbo et al. (1993), Nairn et al. (1989), and Sultan and Braitenberg (1993). Figure 1 courtesy of Dr. Fahad Sultan, Tübingen.

In Fig. 1 granular cell density (number of cells per unit volume of the granular cell layer) is plotted against the size of the entire cerebellum for five different mammalian species.In log-log coordinates the relation appears fairly flat, conforming to our case I. The solid line is the regression line, while the three dashed lines show the expected dependency of cell density on volume according to our hypothetical cases I, II, and III.

It should be noted, however, that Purkinje cells, the other striking neuronal population in the cerebellum (even if several thousand times less numerous than granular cells), follow a different rule. Their density decreases with larger cerebella, and their number is proportionate to the 0.627th power of cerebellar volume (Mwamengele et al., 1993). Thus in the cerebellar cortex our two cases I and II coexist, being represented by two different neuronal populations.

Case II predicts quantitative relations between number of neurons and neural density, as well as between number of neurons and brain volume that have long since been established in the comparative anatomical literature. Shariff (1953), Tower (1954), and Bok (1959)—all quoted in Jerison (1973)—found a proportionality between neuronal density in the cerebral cortex (number of neuronal cell bodies per unit volume) and the inverse of the cubic root of brain weight (volume), just as predicted by our model.

The proportionality between the number of neurons and the 2/3 power of brain weight, being a mathematical consequence of this, was also established experimentally (Shariff, 1953; Jerison, 1963).

In Fig. 2 brain volume is plotted against total number of neurons for five mammalian species, the same as on Fig. 1. The total number of neurons was computed from available data on neuronal density and volume of the grey substance (Sholl, 1956; Cragg, 1967; Blinkov and Glezer, 1968; Frahm et al., 1982; Schüz and Palm, 1989; Braitenberg and Schüz, 1998). Quite convincingly, the measured data in subhuman mammals follow the 3/2-power dependence predicted by our case II. Only the human brain appears to excel among the others with a number of neurons in excess of what the general law would assign to it.

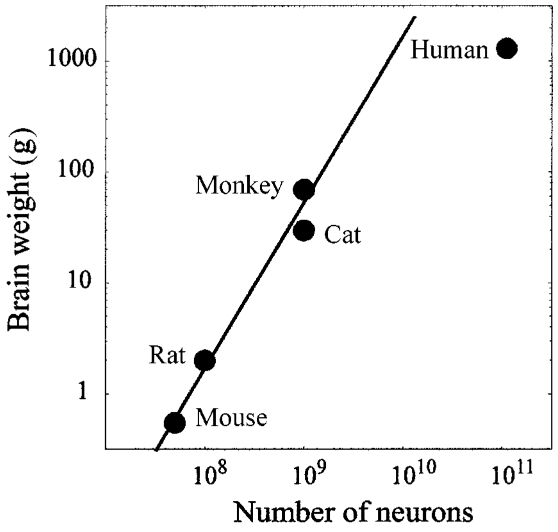

Figure 2. Brain weight plotted against total number of neurons for five mammalian species (the same as on Fig. 1). Except for the human brain, the others comply to the proportionality between volume and the 3/2 power the total number of neurons. The number of neurons was computed from available data on neuronal density and volume of the cortex, multiplied by a factor of 4 to accommodate the neurons in the basal ganglia, in the brain stem, and especially in the cerebellar cortex, which together we estimate to be three times as numerous as the cortical neurons. Data from Sholl (1956), Cragg (1967), Blinkov and Glezer (1968), Frahm et al. (1982), and Braitenberg and Schüz (1998).

It is interesting to test our scheme against reality in absolute values. With 10^{10} neurons such as a large primate might have, our formula yields a volume of 10^{15} $\mu\text{m}^3 = 10^6$ mm^3, corresponding to a linear dimension of 10 cm, quite in accordance with reality. With the 10^8 neurons of the rat, the volume turns out to be 10^{12} μm^3 $= 10^3$ mm^3, corresponding to a side of 1 cm, again quite close to reality.

Our *case III* is unrealistic. The dependence of brain volume on the third power of the number of neurons leads to impossibly large volumes even if very conservative estimates are made on the thickness of the fibers. With the cross-sectional area of all fibers $a = 1$ μm^2, which we had assumed, and a number of neurons of the order of 10^{10}, as in humans, we get a brain volume of 350 cubic kilometers. Even in the mouse with its 10 million neurons, the volume of a complete set of connections between neurons would occupy about 350 cubic meters. It is doubtful whether perhaps some small piece of nerve tissue somewhere in some brain is built according to the scheme of complete neuron-to-neuron connections, but if such an organ exists, it must be very small indeed. One thousand neurons, fully connected, would occupy a volume of 0.35 cubic millimeter, a reasonable size for a small ganglion.

Case IV was proposed originally (Braitenberg, 1978; Braitenberg and Schüz, 1998) as a remedy against the obvious pathology of case III as applied to the cerebral cortex. The idea of square root compartments is appealing for various reasons. First of all, the size of these compartments (portions of the cortex containing $N^{1/2}$ neurons, about 1 mm in humans and 0.17 mm in the mouse) is similar to the size of compartments that were described as "cortical columns" by physiologists on the basis of their responses to sensory stimuli. Also, the dendritic spread of the largest neurons corresponds well to the size of square root compartments both in the human and the mouse brain. Finally, a rough estimate of the volume of the white substance underlying the human, monkey, and mouse cortex was well compatible with the supposition of a complete set of connections between compartments in all three species (Braitenberg, 1978). This is astonishing, especially in view of the fact that the hemispheric white substance is organized in rather well-defined bundles that do not seem to conform to a scheme of homogeneous all-to-all connections. Possibly, the bundling of fibers that have a similar origin and destination into macroscopic “fiber tracts” is a secondary effect, more related to processes of growth than to the statistics of cortico-cortical connections.

It should be noted that the idea of square root compartments in our previous publications, and also in the form presented here, leads to an estimate of the number and length of cortico-cortical connections—that is, to the volume of the hemispheric white substance, disregarding the volume of the fiber felt within the compartments. In a review of data derived from 59 mammalian species, Zhang and Sejnowski (2000) showed that the volume of the cortex is proportional to the 3/4 power of the volume of the hemispheric white substance across the entire range from the shrew to the elephant. Together with the 3/2 power dependence of the volume of the white substance on the number of neurons that we postulate here, this yields a 9/8 power dependence of cortical volume on the number of neurons. Translated into ordinary neuroanatomy, this means that the grey substance of the cortex stays behind the overall increase of brain volume with increasing number of neurons: the contribution of cortical neurons to brain volume is mainly in their long-distance axons.

4. Discussion

This is not the place to embark on a discussion of the reliability of comparative anatomical data. Measurements of brain weight are often flawed by different methods of fixation, by different anatomical definitions (such as brain with or without brain stem), and by unspecified ages of the animals. Even more problematic are the estimates of numbers of neurons, since to go from counts of neurons in microscopic sections to their number in the volume requires sophisticated methods that have not always been respected in the past. However, when the aim is to arrive at dependences in the form of “power laws” appearing as straight lines on log-log plots such as our Figs. 1 and 2, much of the experimental uncertainty usually fades in the face of the overall rule. This has been convincingly demonstrated in the masterful monograph by H.J. Jerison (1973), which we take as our lead. As an inexhaustible source of comparative material, Blinkov and Glezer (1968) should also be recommended.

The most astonishing fact in the comparison of our abstract models with reality is their good fit in special cases, in spite of the very rough approximations they are based on. The quite arbitrary assumption of an overall fiber thickness of 1 μ together with the total neglect of the contribution of neural cell bodies, glia, and blood vessels to brain volume seem to add up to a reasonable compromise. If fibers on an average are less than 1 μ thick in real brains, as they certainly are, it seems that the supporting tissue elements, including neural cell bodies, add a volume proportionate to their length, so that the total volume comes out to be that of a system of naked fibers of about 1 μ thickness. The real contributions of neural cell bodies, axons, dendrites, glia, and blood vessels to the volume of the gray substances can be assessed on electronmicrographs—for instance, in the cerebral cortex of the mouse (Braitenberg and Schüz, 1998). The measured volumes are: axons 29.3%, dendrites 30.2%, dendritic spines 12.06% (sum of “fibers” in the sense of this article 72%), glia 9.5%, cell bodies and blood vessels 13.8%, and extracellular space 5.2%.

Our schemes I, II, and IV have their counterparts in different parts of real brains and therefore presumably indicate different kinds of information handling. Some very general statements can be made about them.

Scheme I is compatible with local interactions between neighboring elements, without any contribution from the activity of more distant elements. One expects and indeed finds (for example, in the visual ganglia of insects) such networks in the proximity of some input layer, where they act as the first filter performing homogeneous local transformations on the input. Why such a scheme is also realized in the cerebellar cortex, what the elementary transformation is, and on what input-space neighbourhood is defined there are still matters of debate (Braitenberg et al., 1997).

Scheme II describes a situation in which every neuron can in principle receive information by direct fibers from every part of the brain, but the probability of a direct connection between any pair of neurons decreases with the size of the brain. This implies that relevant patterns of activity (that is, such patterns as can propagate) must involve more neurons in larger brains. In the light of a theory of cell assemblies (Hebb, 1949), we expect neuronal assemblies (that is, sets of neurons which tend to fire together and represent the units of information transmission) to be composed of a larger number of neurons in larger brains. Larger brains handle more complex internal objects or concepts.

Scheme IV is quantitatively similar to scheme II, with the difference that the relevant units of activity are housed in separate "compartments." One would then expect a certain degree of homogeneity of the responses of single neurons within a compartment, and this is indeed what led physiologists to the idea of "cortical columns" in the first place, making the identification of our abstract compartments with the physiological columns quite tempting. In general terms of brain semantics, the idea of compartments implies a two-stage definition of meaning in the brain, within compartments and between compartments. In reality, it may be a three-stage process if we consider "cortical areas," the well-known subdivisions of the cortex defined by their different sensory input or by the different context in which they analyze the same input (specialized areas for the detection of visual form or visual movement, for acoustic analysis in the context of language, and so on). These areas in humans have a size of a few centimeters, intermediate, on a geometric scale, between cortical columns (millimeters) and the whole cortex (decimeters).

A generalization of the idea of compartments to a hierarchy of k levels, each level containing $N^{1/k}$ compartments of the next lower level, was proposed by Perelmouter (2000). With $k = 4$, the volume of the connecting fibers masses turns out quite realistically to be proportionate to the 3/2 power of N.

Final comment: The assumption of a constant average thickness, and hence constant average conduction velocity of the fibers in brains of different sizes, implies an increase of conduction times in larger brains. This may well be compensated by thicker, faster-conducting fibers, which will in turn contribute more strongly to brain volume. This is an important point raised by Ringo (1991, 1994) and fits some data on the distribution of fiber diameters in the corpus callosum of mouse and monkey (Schüz and Preissl, 1996). We have disregarded these considerations in our crude models, mainly because the average caliber of the fibers does not seem to vary much between animals of different sizes. Also, the increase in the times of neuronal processing, which should be proportionate to the diameter of the brain—that is to the 2/3-power of the length of the body (the volume of the brain being proportionate to the surface of the body)—could be partly compensated by the increase of the mechanical time constants of movements, which may be assumed to vary as the period of a pendulum (that is, proportionate to the square root of the length).

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References

Andersen BB, Korbo L, Pakkenberg B (1992) A quantitative study of the human cerebellum with unbiased stereological techniques. *J. Comp. Neur.* 326:549–560.

Blinkov SM, Glezer II (1968) *The Human Brain in Figures and Tables.* Basic Books, New York. (Russian original: *Mosg cieloveka v cifrach i tavlicach*, Medicina, Leningrad, 1964).

Bok ST (1959) *Histonomy of the Cerebral Cortex.* Van Nostrand-Reinhold, Princeton, N.J.

Braitenberg V (1977) *On the Texture of Brains*. Springer-Verlag, New York.

Braitenberg V (1978) Cortical architectonics, general and areal. In: M Brazier, H Petsche, eds. *Architectonics of the Cerebral Cortex.* Raven, New York.

Braitenberg V, Heck D, Sultan F (1997) The detection and generation of sequences as a key to cerebellar function: Experiments and theory. *Behavioral and Brain Sciences* 20:229–277.

Braitenberg V., Schüz A (1998) *Cortex: Statistic and Geometry of Neuronal Connectivity* (2nd ed.). Springer-Verlag, New York. (revised edition of *Anatomy of the Cortex: Statistics and Geometry*, Springer-Verlag, 1991).

Caddy KWT, Biscoe TJ (1979) Structural and quantitative studies on the normal C3H and lurcher mutant mouse. *Phil. Trans. R. Soc. London B* 287:167–201.

Cragg BG (1967) The density of synapses and neurons in the motor and visual areas of the cerebral cortex. *J. Anat*. 101:639–654.

Frahm HD, Stephan H, Stephan M (1982) Comparison of brain structure volumes in Insectivora and primates. I: Neocortex. *J. Hirnforschung* 23:375–389.

Harvey RJ, Napper RMA (1988) Quantitative study of granular and Purkinje cells in the cerebral cortex of the rat. *J. Comp. Neurol.* 274:151–157.

Hebb DO (1949) *Organization of Behaviour.* Wiley, New York.

Jerison HJ (1963) Interpreting the evolution of the brain. *Human Biol.* 35:263–291.

Jerison HJ (1973) *Evolution of the Brain and Intelligence*. Academic Press, New York.

Korbo L, Andersen BB (1995) The distributions of Purkinje cell perikaryon and nuclear volume in human and rat cerebellum with the nucleator method. *Neuroscience* 69:151–158.

Korbo L, Andersen BB, Ladefoged O, Moller A (1993) Total numbers of various cell types in rat cerebellar cortex estimated using an unbiased stereological method. *Brain Res.* 609:262–268.

Mugnaini E (1983) The length of cerebellar parallel fibers in chicken and rhesus monkey. *J. Comp. Neurol.* 220:7–15.

Mwamengele GL, Mayhew TM, Dantzer V (1993) Purkinje cell complements in mammalian cerebella and the biasses incurred in counting nucleoli. *J. Anat.* 183 (Pt. 1):155–160.

Nairn JG, Bedi KS, Mayhew TM, Campbell LF (1989) On the number of Purkinje cells in the human cerebellum: Unbiased estimates obtained by using the "fractionator." *J. Comp. Neurol.* 290:527–532.

Perelmouter J (2000) Private communication.

Ringo JL (1991) Neuronal interconnection as a function of brain size. *Brain, Behavior and Evolution* 38:1–6.

Ringo JL (1994) Time is of essence: A conjecture that hemispheric specialization arises from interhemispheric conduction delay. *Cerebral Cortex* 4:331–343.

Schüz A, Palm G (1989) Density of neurons and synapses in the cerebral cortex of the mouse. *J. Comp. Neurol.* 286:442–455.

Schüz A, Preissl H (1996) Basic connnectivity of the cerebral cortex and some considerations on the corpus callosum. *Neuroscience and Biobehavioral Rev.* 20/4:567–570.

Shariff GA (1953) Cell counts in the primate cerebral cortex. *J. Comp. Neurol.* 98:381–400.

Sholl DA (1956) *The Organization of the Cerebral Cortex*. Wiley, New York.

Sultan F, Braitenberg V (1993) Shapes and sizes of different mammalian cerebella: A study in quantitative comparative neuroanatomy. *J. Hirnforschung* 34:79–92.

Tower DB (1954) Structural and functional organization of mammalian cerebral cortex: The correlation of neuron density with brain size. *J. Comp. Neurol.* 101:19–51.

Zhang K, Sejnowski TJ (2000) A universal scaling law between gray matter and white matter of cerebral cortex. *Proc. Nat. Acad. Science* 97:5621–5626.