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Constancy and Variability in Cortical Structure.
A Study on Synapses and Dendritic Spines in Hedgehog and Monkey

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With 5 Figures and 2 Tables

Summary: Synapses and dendritic spines were investigated in the parietal cortex of the hedgehog *(Erinaceus europaeus)* and the monkey *(Macaca mulatta)*. There was no significant difference in the density of synapses between the two species (14 synapses/100 μm^2 in the hedgehog, 15/100 μm^2 in the monkey), neither in the size of the synaptic junctions, in the proportion of Type I and Type II synapses (8–10 % were of Type II in the hedgehog, 10–14 % in the monkey) nor in the proportion of perforated synapses (8 % in the hedgehog, 5 % in the monkey). The only striking difference at the electron microscopic level concerned the frequency of synapses in which the postsynaptic profile was deeply indented into the presynaptic terminal. Such synapses were 10 times more frequent in the monkey.

Dendritic spines were investigated in Golgi-preparations. The density of spines along dendrites was similar in both species.

The results are discussed with regard to connectivity in the cortex of small and large brains.

Key words: allometry, connectivity, brain size, associative cortex, pyramidal cells.

Introduction

One approach of obtaining insight into the relationship between structure and function of the brain is to compare brains of different species with regard to their behaviour. Structural differences might reveal how different types of behaviour are built into the brain. Similarities in structure, on the other hand, can tell us something about basic properties of information processing in a given part of the brain.

Another factor which has an impact on the structure of the brain is brain size. Some of the relationships between fine structure and brain size are relatively well-known. For example, the density of neurons in the cortex decreases with brain size in a regular manner (summarized in Jerison 1973). The average dendritic length of neurons, on the other hand, increases with brain size (Bok 1959). A prerequisite for the functional interpretation of the fine structure of the brain is the knowledge of such allometric rules.

It is not yet well understood how the density of synapses varies with brain size and/or complexity of behaviour. The synaptic densities found in the literature for the cerebral cortex of various mammalian species vary between $2.8 \times 10^8/mm^3$ and $1.3 \times 10^9/mm^3$ (summarized in Colonnier 1981, Peters 1987). However, a clear correlation with brain size or with complexity of behaviour cannot be inferred from these data and it is probable that at least some of the variability is due to differences in the methods used by the various authors.

In the present study we investigated the density of synapses in the neocortex of the hedgehog *(Erinaceus europaeus)* and the rhesus monkey *(Macaca mulatta)*. These species are representatives of two groups which can be considered as two extremes with respect to brain development: the insectivores are the group deviating least from the early placental ancestors with respect to both anatomy and behaviour, while in the group of primates the strongest increase in relative brain weight and in complexity of behavior has occurred. Thus these two groups are interesting for comparative studies (Stephan 1972, Frahm et al. 1982, Stephan 1983, Stephan et al. 1986), since they can be expected to reveal the range of variability in the structure of the mammalian brain.

Our material was taken from an associative region of the parietal cortex, from area 5/7 according to Brodmann (1909). In the hedgehog, this area is situated in the middle third of the cortex (in rostro-caudal direction) rostrally adjacent to the auditory cortex. The homology of this region in the two species is based on similarities in cytoarchitectonics, in thalamocortical input and in certain electro-

physiological features (BATUEV et al. 1980). In both species, this region has already been compared with respect to a number of other anatomical properties, such as size of neurons and shape of dendritic and axonal arborizations (DEMIANENKO 1977, 1978, 1980).

In addition to the density of synapses, we examined some further synaptic measures which are interesting in connection with allometry or behaviour: the size of synapses, the proportion of symmetric and asymmetric synapses and the proportion of perforated synapses.

Since we had Golgi-preparations from these areas in both species at our proposal, we also compared the density of dendritic spines. Spines are known to be the main sites of synapses on pyramidal cell dendrites and therefore make it possible to investigate the distribution of synapses along dendrites by way of the light microscope. One may ask, for example, how the greater dendritic length of individual neurons in larger brains affects the density of spines. Dendritic spines are, furthermore, believed to play a role in learning processes, a function which may be more prominent in the primate brain than in that of insectivores.

Methods

Electron microscopy

Electron microscopic preparations were made from two adult hedgehogs *(Erinaceus europaeus)* and two adult rhesus monkeys *(Macaca mulatta)*. They were fixed in 2% glutaraldehyde and 0.5% paraformaldehyde in 0.2 M phosphate buffer at pH 7.4. The hedgehog brains were fixed by perfusion (after anesthesia with a lethal dose of Nembutal) and small blocks of tissue were cut out shortly after perfusion. The tissue from the monkey brains was gained from animals which had been part of a chronical electrophysiological experiment. The skull was opened under deep anaesthesia shortly before the animal was sacrificed, the fixative was dripped onto the region to be investigated and after a fixation time in situ, comparable to that in the hedgehog, small blocs of tissue were cut out. (The relatively large amount of extracellular space resulting from the fixative used as well as the different initial treatment of the two species will be delt with in the discussion part of this paper).

The tissue blocs from both species were kept in fixative for 3 hours. Postfixation was carried out in 2% OsO₄ in phosphate buffer. After several washes in phosphate buffer and then in distilled water, the blocs were placed in 1.5% uranyl acetate in distilled water for 1 hour. After dehydration in a graded series of ethanol over a time span of 3 hours, they were transferred to several changes of ethanol/propylen oxide for a total of 1 hour and then embedded in Epon. The thin sections were contrasted with lead citrate. In the electron microscope, pictures were taken through layers II/III at a magnification of 12400. Evaluation was made at a final magnification of 30000.

Counts were made on 115 electron micrographs in one monkey and on 34 electron micrographs in the other. On each picture, a region of 50 µm² was evaluated. In the hedgehog, the corresponding numbers were 90 electron micrographs in one animal and 32 in the other.

Since a possible difference in the size of the synapses between the two species could influence the number of synapses counted on the quasi two-dimensional sections, the average size of synapses was also determined. This was done by measuring the length of the postsynaptic thickening. If the synaptic junction was curved, the chord between the two ends of the postsynaptic thickening was measured since this is the measure which is relevant for stereological correction of synaptic density (e.g. SCHÜZ and PALM 1989). If the synapse was positioned more or less in parallel to the section, the largest diameter of the postsynaptic disc was measured.

Classification into symmetric and asymmetric synapses was carried out on the basis of the presence of a postsynaptic thickening (COLONNIER 1968). This criterion can be reliably applied only in synaptic junctions which are oriented in the section such that the synaptic cleft is clearly visible. Therefore, only these synapses were used for the determination of the synaptic type.

Some synapses are charcterized by a postsynaptic disc which has one or sometimes several holes (PETERS and KAISERMAN-ABRAMOF 1970, CALVERLY and JONES 1987). The percentage of this kind of synapses was also determined.

Light microscopy

We had at our disposal Golgi-preparations from 15 hedgehogs and 10 monkeys. The majority of these were Golgi-Kopsch preparations, the others Golgi-rapid preparations (ROMEIS 1968). Those preparations in which the spines were best stained were selected for spine counts, at least two from each method in each species. All preparations were embedded in celloidin and cut at a thickness of 100 to 150 µm.

Spine counts were made on basal dendrites of pyramidal cells, the cell bodies of which were situated in layers II, III and V. Dendritic pieces were chosen according to the following criteria: they had to lie close to the surface of the section so that spines were well discernible, and the pieces had to be oriented more or less in parallel to the section. The pieces collected on this basis had lengths between 35 and 75 µm. Spine free proximal pieces were disregarded. A correction for spines hidden by the dendrite was not applied. An objective lens with aperture 0.75 was used.

Results

a) Synapses

The areal density of synapses was quite similar in monkey (14.9 synapses/100 µm²) and hedgehog (13.8/100 µm², see also Table 1). The same holds true for the average size of the synapses as measured on the electron micrographs: 379 nm in the monkey and 357 nm in the hedgehog. As one can see from Table I, the average synaptic size in the two hedgehogs overlaps with those in the monkeys, indicating that there is no systematic difference between the two species.
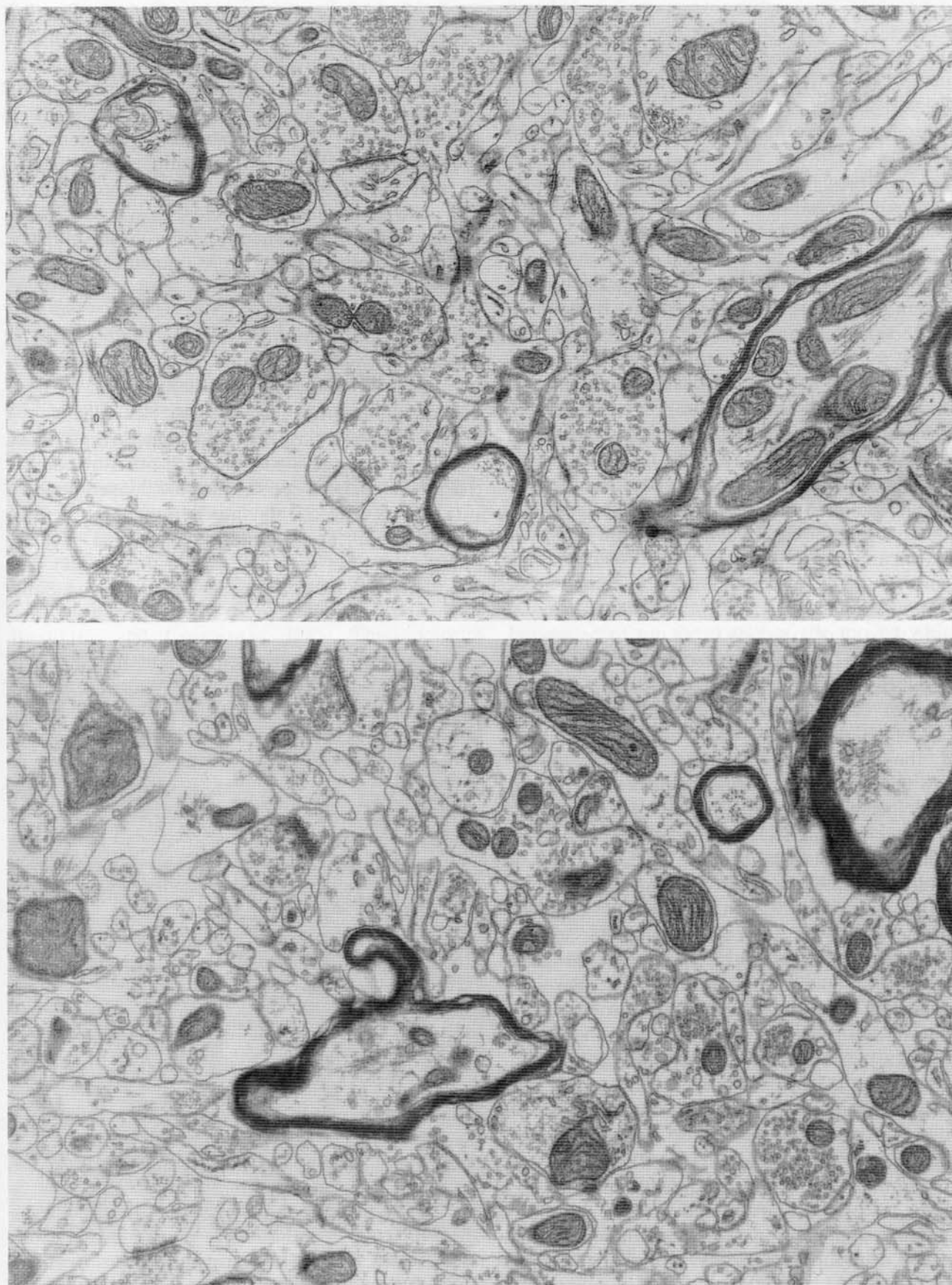
Fig. 1. Electron micrographs from the neuropil of layer III of the cortex of the monkey (a) and the hedgehog (b). Bar: 1 μm.

Table I.

	no. of synapses/50 μm²		size of synapses (nm)	
	mean and standard deviation	no. of measurements	mean and standard deviation	no. of measurements
Hedgehog 1	6.2 (±2.6)	90	373 (±146)	338
Hedgehog 2	7.5 (±2.2)	32	340 (±135)	128
Monkey 1	7.5 (±2.7)	115	364 (±131)	550
Monkey 2	7.4 (±3.0)	34	394 (±138)	158

This frees us from the necessity of transforming the counts of synapses made on the two-dimensional sections into number of synapses per volume. However, in order to be able to compare our counts to those of other authors, we did make an estimate of the number of synapses per mm³. As a first step, one has to correct the synaptic size measured on the electron microscopical sections, since these are much thinner than most of the synaptic junctions and therefore often do not include the full synaptic diameter. Using the formulae presented in the paper by SCHÜZ and PALM (1989), our results lead to a real synaptic size of about 460 nm in the monkey, and of 430 nm in the hedgehog[1]. With this synaptic size the volume density of synapses turns out to be around 3×10^8/mm³ in both species (using formula 1' of the same paper, developed by MAYHEW, 1979).

Most of the synapses were of the asymmetric type. Depending on the strictness of the criteria used, the percentage of symmetric synapses was 8–10% in the neuropil of the hedgehog, and 10 to 14% in the monkey. The difference between both species was not statistically significant (t-Test), nor was there a significant difference in the number of perforated synapses. In the hedgehog, it was 8% and in the monkey 5% of the synapses.

On the whole, the neuropil had a similar appearance in both species (Fig. 1). One might have expected the dendrites and axons to be thicker in larger brains. Were this the case, the neuropil should contain thicker profiles and therefore have a coarser appearance in the monkey. As far as could be seen by qualitative means, this was not the case. This speaks in favour of a similar average diameter of dendrites and axons in the cortical neuropil of both species.

The monkey cortex possessed, however, one conspicuous feature: the postsynaptic profile was quite often deeply indented into the presynaptic terminal (Fig. 2). Correspondingly, the synaptic junction was

often strongly concave on the presynaptic side. The concavity was, however, not restricted to the synaptic junction. The presynaptic terminal frequently formed a tongue-like process which wrapped around the postsynaptic profile, sometimes enclosing it completely (Fig. 2 c). If we took as a criteria the requirement that the postsynaptic profile had to be surrounded for at least half of its outline by the presynaptic one, such "closed" synapses made up about 10% of the synaptic profiles in the monkey, and were about 10 times more frequent than in the hedgehog.

b) Dendritic spines

The basal dendrites of pyramidal cells in hedgehog and monkey are similar in appearance (Fig. 3) and cannot be distinguished from each other by qualitative means. In both species they are densely covered with spines. The counts showed a small, but statistically significant difference in spine density (Table II): it was slightly higher in the monkey preparations (p = 0.01, test of Kolmogoroff and Smirnoff).
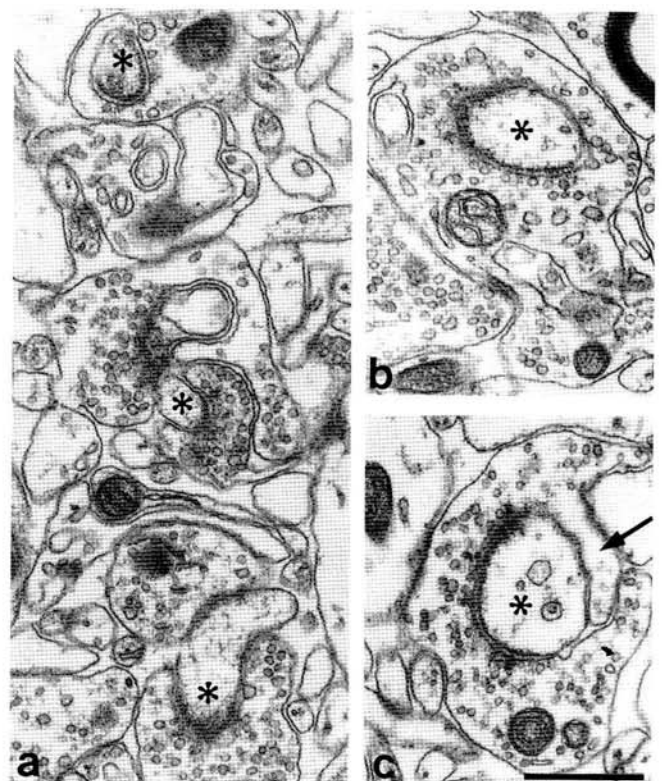

Fig. 2. Electron micrographs from the cortex of the monkey, showing some examples for synapses in which the postsynaptic profile (asterisks) is deeply indented into the presynaptic terminal. In c) a presynaptic profile is shown which encloses the postsynaptic one by way of a tongue-like cytoplasmatic process (arrow). Bar: 0,5 μm.

[1] (taking a typing error in formulas 2' and 3' in this paper into account: the factor 1/2 has to be replaced by 2/π.) monkey preparations (p = 0.01, test of KOLMOGOROFF and SMIRNOFF).

Table II.

| | no. of spines/μm of dendritic length | | |
	mean and standard deviation		no. of measurements
Hedgehog	0.71	(±0.22)	46
Monkey	0.86	(±0.20)	129

Discussion

Density of synapses

Although the hedgehog and the rhesus monkey differ considerably in both brain size and behaviour, their brains do not differ significantly with respect to the density of synapses in the cortex. This suggests that the density of synapses is quite constant throughout the group of mammals.

Findings of other authors point in the same direction. The variance in the density of synapses to be found in the literature in various species is considerably reduced (to a factor of 1.5 at most) if one sticks to those results which have been obtained by the same authors using the same methods (CRAGG 1967, BEAULIEU and COLONNIER 1985). This indicates that the variance in the synaptic density reported in the literature for different species is largely due to variables such as tissue shrinkage, stereological methods and the criteria used for the classification of synapses, rather than to true interspecific variation.

The fact that the density of synapses is rather constant is also evident when comparing different cortical areas in the same species. In the mouse, it varies by less than a factor of 1.3 (SCHÜZ and PALM 1989). The same is true when comparing the same area in different individuals of one species. Similar results have been obtained by VRENSEN (1978) in the rabbit, and by CRAGG (1967) in mouse and monkey. The latter author found, however, a somewhat higher density of synapses in the motor than in the visual cortex in both species (by a factor 1.3 in the mouse and 1.5 in the monkey).

The largest difference in synaptic density which has been found is between the left and right hemisphere (VRENSEN and DE GROOT 1974, 1975). In certain parts of the visual and motor cortex the density of synapses differed by a factor of 2 between the two sides. It is intriguing to relate this to left-right differences in cortical function. For example, lower synaptic density might be a side-effect of thicker neuronal processes. A difference in fiber thickness between left and right hemisphere as a basis for lateralization of function has been proposed (MILLER 1987).

Number of synapses per neuron

In contrast to the density of synapses, the density of neurons differs considerably with brain weight: larger brains have a lower density of neurons. This implies that the average number of synapses per neuron must increase with brain weight. It is not yet possible to give exact numbers, since there is disagreement about the exact correlation between density of neurons and brain weight (JERISON 1987). According to the older literature, the density of neurons varies with brain weight to the power of about -1/3 (TOWER 1954). This would mean that a small brain like that of a mouse would have a 10 times higher density of neurons than for example the human brain (which is about 1000 times heavier). According to more recent literature, the density of neurons varies, however, only proportionally to cortical thickness (ROCKEL et al. 1980). In this case, the density should not vary by more than a factor of 4, since the thickness of the human cortex is about 3 to 4 times that of the mouse (BLINKOV and GLEZER 1968; ROCKEL et al. 1980). At present, we can therefore only say that the human cortex must have at least 3 and at most 10 times more synapses per neuron than the cortex of the mouse which is known to have an average of 8000 synapses per neuron (SCHÜZ and PALM 1989, BRAITENBERG and SCHÜZ 1991). Considerations by STEVENS (1989) speak in favour of the lower range between the two values.

Another quantity which seems to be allometrically constant is the total dendritic length per mm^3 of cortex (JERISON 1973). This can be concluded from BOK's data (1959) which suggest that the total dendritic length per neuron increases by about the same factor as the density of neurons decreases with brain weight. This has led to the assumption that the amount of information which can be processed per unit volume of cortical tissue is the same throughout the group of mammals (JERISON 1973), and that cortical volume is therefore a good measure for the total amount of information which can be processed in the cortex of a certain species. A crucial point in this reasoning was the assumption that there is a constant density of synapses per dendritic length in different species. If both dendritic length and number of synapses per volume are constant, this must indeed be the case.

This is in a way also confirmed by the *spine counts*, although the density counted in the hedgehog turned out to be slightly lower than in the monkey in our preparations. The counts show in any case that a larger dendritic length per neuron, as the monkey must have, is not accompanied by an increase in the
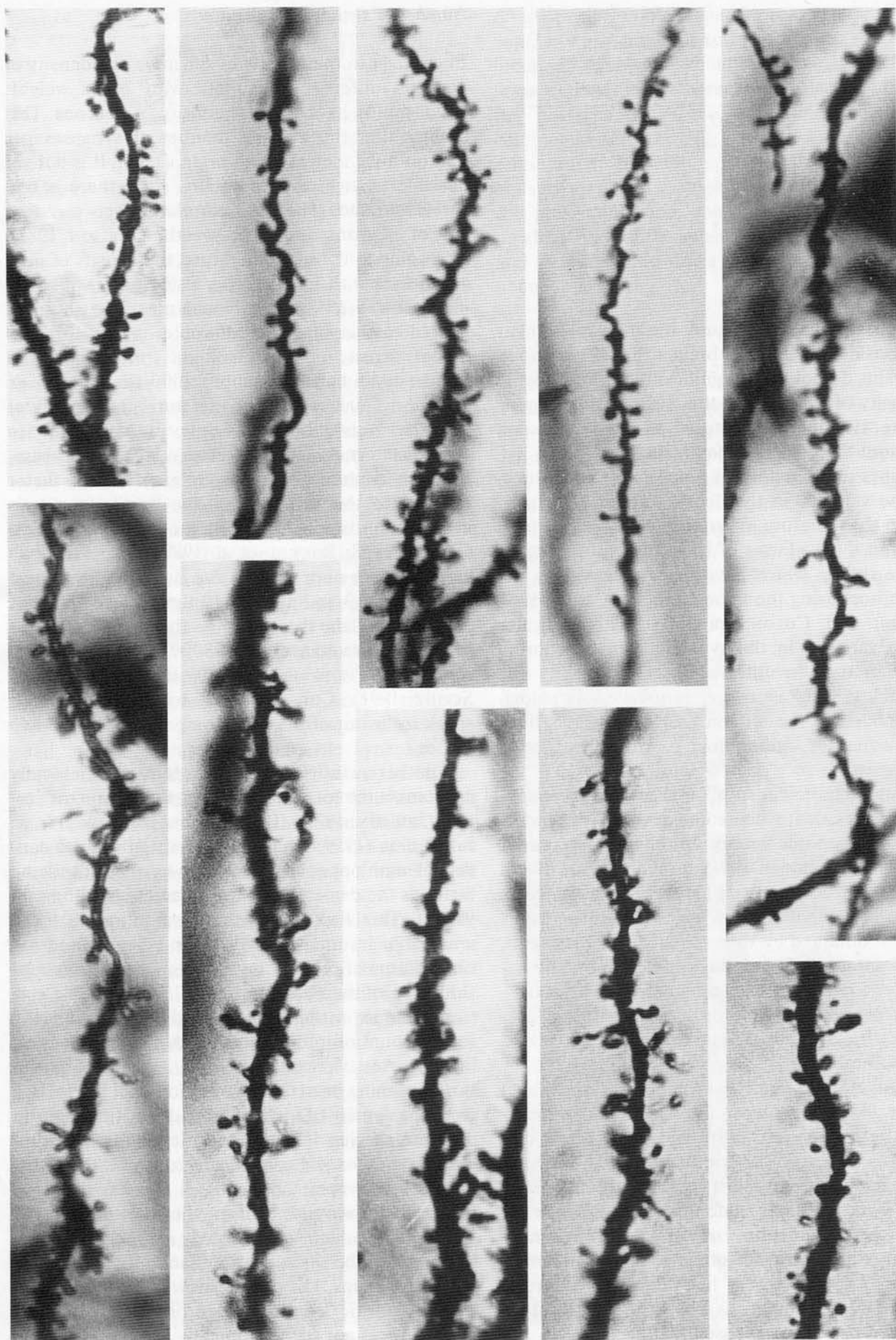
distance between spines. Since the majority of synapses on pyramidal cell dendrites is located on spines, the density of spines is a rough measure for the arrangement of synapses along dendrites.

Another way of putting the above argument is to say that the number of bits which can be stored in a unit of cortical volume is constant, sinde there is good reason (e. g. HEBB 1949, HUBEL and WIESEL 1965, PALM 1981) to assume that the place of storage of information is the synapse rather than the neuron as a whole.

The allometric behaviour of the neuropil is summarized in Fig. 4.

With increasing brain size:

Density of neurons:	↓
Length of axons and dendrites per mm³:	−
Length of axons and dendrites per neuron:	↑
Density of synapses per mm³:	−
Density of synapses along axons and dendrites:	−
Synapses per neuron:	↑

Fig. 4. Summary of increasing (↑), decreasing (↓) or constant (−) properties in the neuropil of the cerebral cortex with increasing brain size.

Divergence and convergence between neurons

What is the significance for a neuron that it has more synapses? First of all, one has to clarify whether neurons with more synapses also have more synaptic neighbours, or whether they connect to the same number of neurons as in a small brain but via more synapses. As shown in the mouse, the cortical network is characterized by a high degree of divergence and convergence between pyramidal cells (CRAGG 1967, BRAITENBERG 1978 a). One would like to know if the degree of divergence and convergence increases with an increasing number of synapses per neuron, or if it stays constant throughout the group of mammals. A prerequisite for the first assumption is that in a larger brain the pyramidal cells ramify in a larger volume of cortex and thus reach (and can be reached by) a larger number of neurons. Let us now assume that the density of neurons in a large brain such as the human one is 1/4 of that in a brain as small as that of the mouse and that, correspondingly, the average pyramidal cell in the human brain has 4 times more synapses. If such a pyramidal cell is to connect to 4 times more neurons than a pyramidal

cell in the mouse cortex, it would have to ramify within a volume which is $4 \times 4 = 16$ times larger (Fig. 5). Assuming this volume would have the shape of a cube, the side of this cube would have to be 2.5 times larger in the human than in the mouse cortex. It is known that in larger brains the dendritic trees of pyramidal cells have, on average, a larger diameter and thus ramify within a larger volume. In mice, BOK (1959) has measured an average diameter of basal dendritic trees of pyramidal cells of 130 μm and in rabbits (the largest brains he investigated) an average of 226 μm, thus a difference by a factor of 1.74. We do not have corresponding measurements on the human cortex. It is known, however, that the dendritic trees of large pyramidal cells in humans can reach a diameter of 1 mm (POLJAKOW 1973, BRAAK and BRAAK 1976). From the paper by BUELL and COLEMAN (1981) one can conclude that pyramidal cells in layer II of the human cortex reach diameters of 450 μm. An average increase from mouse to man of a factor of 2.5 (or more) is therefore quite probable. Thus, as far as one can conclude from the dendrites, the size of the neurons increases so that the supply of possible synaptic neighbours increases correspondingly. This suggests that the degree of divergence and convergence between cortical neurons increases as the number of synapses per neuron does.

This is relevant in connection with the role of the cortex as an associative memory in which correlations in the outside world are learned by strengthening the connections between those neurons which are active simultaneously (HEBB 1949). In order to be able to learn every possible correlation in the outside world, a good overall connectivity of the network is required. It is clear that overall connectivity is more of a problem in a large cortex than in a small one (RINGO 1991). A larger number of connections on the average neuron certainly helps to minimize this problem.

The degree of divergence and convergence is also interesting in connection with the concept of cell assemblies (HEBB 1949; BRAITENBERG 1978 a, PALM 1982) as well as with the theory of "synfire-chains" as proposed by ABELES (1982). One important point of these theories is the assumption that each neuron can be part of several, perhaps many cell assemblies or synfire-chains. A neuron with more postsynaptic neighbours can be part of more cell assemblies and can therefore lead to a richer spectrum of associations.

◄

Fig. 3. Basal dendrites of pyramidal cells in layer II from monkey (upper row) and from hedgehog (lower row). Golgi-preparations. Bar: 10 μm.
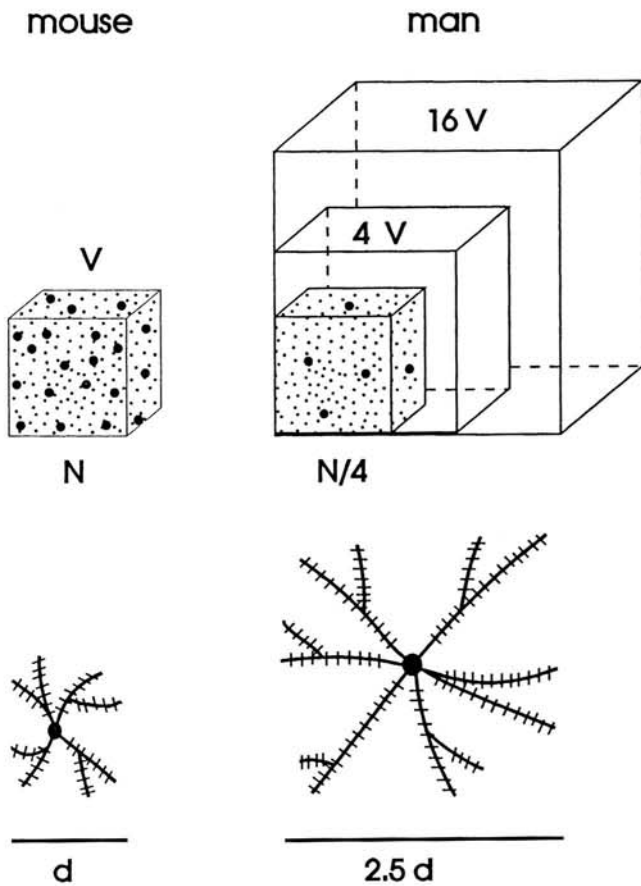
mouse   **man**

Fig. 5. Number of different synaptic neighbours of a neuron in a small and a large brain. As an example, we take the mouse and the human brain and assume the density of neurons in the human brain to be 1/4 of that in the mouse. If the larger number of synapses per neuron (4 times more) in the larger brain are to enable the neuron to reach 4 times more different neurons, its diameter must increase such as to span a volume containing 4 times more neurons. **V** unit volume in a small and a large brain, **N** Number of neurons (large dots). **Small dots:** synapses, **d** diameter of an average dendritic tree.

Excitation and inhibition

One of the reasons why the role of the cortex is seen as an associative memory is the pedominance of excitatory synapses (BRAITENBERG 1978 b). It has been shown, however, that stability in a cortex-like positive feedback network is quite critical (ERB and AERTSEN 1992). The fact that the proportion of *asymmetric* (presumably excitatory) *and symmetric* (presumably inhibitory) synapses was found not to differ significantly suggests that a change in the size of the cortical network is not accompanied by a change in the equilibrium between excitation and inhibition.

"Closed" synapses

A striking difference at the electron microscopic level concerned the frequent occurrence of "closed"

synapses in the monkey. This finding is somewhat puzzling since, to our knowledge, it has not been mentioned in other studies in the monkey and was furthermore less pronounced in a third monkey which we investigated in another context. We were therefore not able within the framework of the present study to determine whether such synapses are typical for the monkey or whether their frequency in these animals had other reasons, for example the experimental conditions preceding the anatomical studies, possibly also the rearing conditions. In spite of this uncertainty we considered it worthwhile to mention this observation which would be interesting in both connections.

In both cases, it is relevant that the degree of curvature of the synaptic membranes, which is quite pronounced in these synapses, has been brought together with learning and with the level of synaptic activity (WENZEL et al. 1977, WESA et al. 1982, VAN HUIZEN et al. 1987, DYSON and JONES 1980, CALVERLY and JONES 1990).

When looking at pictures like Fig. 1, the other aspect of this kind of synapse appears more intriguing: the enclosure of the postsynaptic element. The intimate anatomical coupling between pre- and postsynaptic element suggests a strong functional coupling. The situation is reminiscent of the hippocampus where spines are deeply indented into the presynaptic bags of the mossy fibers. One wonders if these synapses in the cortex perhaps also belong to a particular afferent system which would then be more elaborated in the monkey than in the hedgehog.

Methods

Our values of both synaptic density and density of dendritic spines are at the lower end of the range of what is found in literature for other species and/or areas. We do not believe that this is due to the species or areas investigated, but to the methods used in our study. In the case of the spines, the relatively low density is due to the fact that an objective lens of slightly lower aperture was used than in some other studies (e. g. SCHÜZ, 1976, FELDMAN and PETERS 1979, SCHÜZ 1981). More importantly, a correction for the spines hidden by the dendrite as it was used in these studies was not applied here.

In the case of the synapses, the relatively low densities can be assumed to be due to a lesser degree of shrinkage of the tissue (with dehydration, e. g. SCHÜZ and PALM 1989) or a higher degree of swelling (in Osmium; WILHELMS 1976) as compared to other procedures. The relatively large size of the synapses in our preparations are in agreement with this.

Another indication is the relatively large amount of extracellular space in our preparations. (For the arguments in favour of a higher degree of extracellular space than with the usual methods see Cragg 1979). However, in this study we did not aim at absolute values but at a comparison between two species.

This brings us to the last point: the comparability of the two kinds of preparations. Comparability of histological material is a general problem in species of very different size and behaviour. Equal handling is hardly possible and might even be unfavorable since it might be optimal for one species but stressful for the other. It is, moreover, difficult to figure out which perfusion times and perfusion pressures would correspond to each other in brains of such different sizes. We therefore aimed at the fastest possible fixation method for each species in the given situation rather than at identical initial conditions. Since the two kinds of preparation showed the same degree of preservation of the tissue in the upper layers used for this study, as well as a similar amount of extracellular space, we had no reason to assume a difference in shrinkage of the tissue between the two species which would have influenced the quantitative results.

Acknowledgements

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