

Are Neurons of the Human Cerebral Cortex Really Lost During Aging? A Morphometric Examination*

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Introduction

This description of the aging human brain centers on the biological or physiological aspects of the aging process. All pathologic changes, including presenile dementia, are omitted from the discussion.

Even today, some scientists are still of the opinion that increasing numbers of neurons are lost during life. This belief is based on research published about 30 years ago, the basis of which was the work of Brody (1955). Brody himself expressed this theory of neuron loss in vague terms because his statistical basis was too small to make definite statements. However, subsequent interpretations of his work by other scientists and in the press have created the conviction that neurons are lost throughout life.

Morphometry is the name given to modern and improving procedures of measuring histologic sections. The data obtained in this manner can be transformed into three-dimensional values with the help of stereological techniques which were unknown 30 years ago (Haug 1979; Weibel 1979). These and other new procedures now make possible more efficient methods of examining the question of neuron loss and will also enable other important aspects of brain aging to be described. The following observations concerning brain morphology can be made:

1. Secular acceleration in body size leads to concomitant increases in brain volume for successive generations.
2. Modern procedures allow estimates not only of whole brain weight but also of the volume fraction of gray and white matter for various parts of the brain. With the help of stereology, it is possible to determine whether various parts of the brain undergo changes in size at the same rate.
3. The effect of preparative techniques on morphometric results can be accurately determined in order to correct the morphometric data evaluated and achieve precise results for neuron density and size.
4. Because changes in the ultrastructure of the human brain are difficult to describe, they should be examined by means of electron microscopy. With this method, tissue should be fixed as early as possible after death. However, this is impossible with human brain material because dissection can be performed only after a period of several hours after death.

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Future developments in the preparation of specimens and techniques of measurement can also be expected to lead to good ultrastructural results. Other investigations of aging have been performed by physiologists and behaviorists. Further results gained through animal research can, with caution, be extrapolated to human aging. Some psychological investigations have also opened up new vistas on human brain aging.

All these efforts to increase our knowledge of aging processes require highly sensitive techniques and large quantities of material. This means that future investigations of aging in the human brain will be accompanied by increasing expense. Both the extreme variability of human external and internal structures as well as tissue changes affects results of aging behavior, a fact which also necessitates investigating a large amount of material in order to reach statistical significance. This high variability has made it necessary to revise older measurements which had been based on less material.

Material and Methods

Our investigations of the aging human brain require different types of material. For details concerning the material used in this study to analyze the effect of secular acceleration and aging on brain size, see Haug (1984 b). This investigation was based on the analysis of 24,000 brains.

Changes brought about by aging in various parts of the human brain are evaluated for 12 human brains up to 90 years in age. This relatively small base is attributable to the high expense of this type of investigation (Eggers et al. 1984).

To examine alterations of neuron density and size, we used a large amount of material. A total of five cortical areas were measured:

1. Area 6 in the frontal lobe, which has an extrapyramidal function and has recently been designated the "supplementary motor area" by some investigators
2. Area 11 in the orbital part of the frontal lobe, which is linked to psychosocial functions
3. Area 7 in the convexity of the parietal lobe, which is related to sensory and, especially, speech analysis
4. The projection area 17, or visual cortex, in the occipital lobe
5. Area 20 at the basis of the temporal lobe, which probably plays a role in higher integrative activities. Sharp localization of functions in this area is impossible

Morphometric analyses of neurons were performed on over 120 human brains. A total of 230 single evaluations of brain areas have been made. Each single evaluation resulted in measurements of 1,500–2,000 neurons for all layers. Since details of how these analyses were carried out can be found in Haug (1979, 1982), it is sufficient here to note that each cell was measured over the drawing mirror of a microscope with a computerized digitizer (KONTRON, MOP). This investigation was performed over about 8–9 years.

Effects of Techniques of Tissue Preparation on Morphometric Results

As the procedures used can greatly affect the results obtained, a brief description of methodology is necessary. In this way, the considerable discrepancies in the literature concerning morphological aspects of the aging process might be explained.

Since remarkable change in volume can be observed during the preparation (fixation, dehydration, embedding in paraffin wax, sectioning, and staining) of tissue, we have systematically measured this alteration. Figure 1 shows that the magnitude of these changes during methyl benzoate embedding depends on age. The embedding shrinkage of brain tissue belonging to a young person is more pronounced than for tissue from an older individual, probably because of the different water content.

The increased shrinkage of young tissue tends to compress the neurons on the stained slide, resulting in higher cell density in the microscopic image. On the other hand, the less pronounced shrinkage of tissue from aged individuals produces a lower neuron density. However, the cell density of both kinds of tissue is distinctly higher than for fresh tissue. The difference in embedding shrinkage between tissue specimens taken from individuals 20 and 75 years old amounts to about 15%. Consequently, we observe a 15% lower neuron density in microscopic images of tissue of the aged, making it necessary to estimate the degree of shrinkage in order to be able to correct the primary results.

That embedding shrinkage is age-dependent was unknown to early investigators, who probably correctly counted the number of neurons, but erroneously postulated neuron losses which were in fact caused by differences in the shrinkage of brain tissue (Haug 1980; Sass 1982).

This fact shows that, as in other scientific disciplines, many findings are influenced by the complex reaction of the tissue as a whole. Therefore, results may be falsified if all aspects of the problem are not taken into account. Since it is possible that investigators might not at present be aware of certain factors, erroneous find-

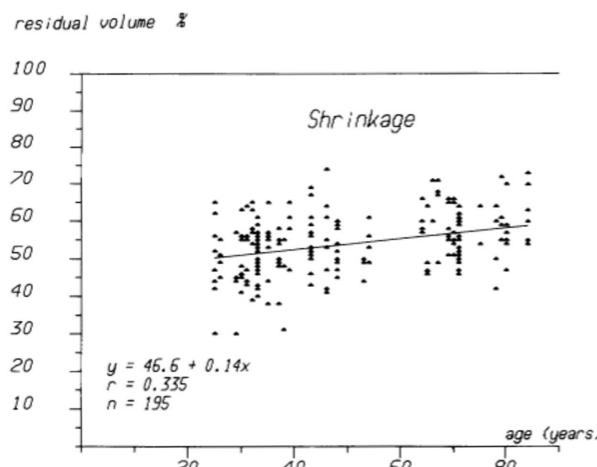


Fig. 1. Brain tissue shrinkage during embedding (expressed residual volume, ordinate) as compared with age. 100% residual volume corresponds to unfixed fresh tissue. The degree of shrinkage is the difference between 100% and the volume of the stained slide. $P=0.001$

ings may result despite the most conscientious efforts. It goes without saying, of course, that we have made an effort to avoid all possible falsifying influences.

Influence of Secular Acceleration on Brain Weight and Aging

Secular acceleration is the increase in human body size from generation to generation. *Developmental acceleration* refers to the accelerated development of a single individual, leading to earlier maturity. The latter process is probably caused by increased standards of living. Because secular acceleration is virtually independent of the living standards, it can be observed in many parts of the world (Haug 1984 b).

The increase in height due to secular acceleration amounts to about 1 mm/year, meaning that mean body height is presently 10 cm greater than 100 years ago. However, it must be noted that the average secular acceleration during the last century represents only half that rate. Human body size remained constant between the birth of Christ and about 1750 A.D.

The larger the body, the larger the brain. Brain weight increases by an average of 0.6 g/year. This means that taking secular acceleration into account, the brain weight of one generation is proportionately higher than that of the preceding generation as measured in youth. Brain weights during one investigation are normally determined within a short time span (transverse examination). Consequently, older generations reveal lower brain weights than subsequent ones, but this lower weight is not actually caused by brain shrinkage.

We have tried to calculate the fraction of the generational difference in brain weights due to secular acceleration, with the aim of estimating the age at which the weight of the human brain actually begins to diminish. Figure 2 shows that the mean human brain weight is constant up to 60 years of age. After the 65 years of age, we can observe a real loss in human brain volume. After the age of eighty,

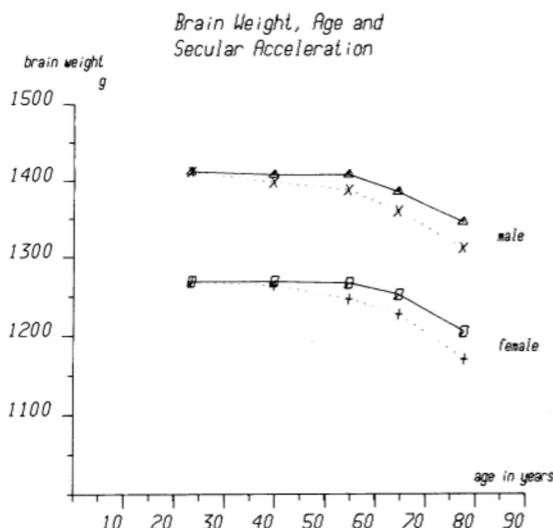


Fig. 2. Mean human brain weight (*ordinate*) as related to age in years (*abscissa*). The *broken line* reflects the average weights for a total of 24,000 brains. The *solid line* takes secular acceleration into consideration and illustrates the change in brain weight occurring during the life span of a hypothetical individual

Table 1. Age-related change in volume of whole human brain and of brain regions expressed in % of the main brain size of a 25-year-old and a 75-year-old person

	Age groups		Brain volume of a 75-year-old as compared with that of a 25-year-old	Change of volume in a 75-year-old relative to a 25-year-old
	30–60 years	61–90 years		
Entire brain	100	100	94	– 6
Entire cortex	48.4	49.3	46.6	– 4
Frontal cortex	15.6	14.5	13.6	– 13
Parietal cortex	16.8	17.8	16.7	± 0
Substantia nigra	31.0	30.8	28.9	– 7
Basal ganglia	3.75	3.31	3.11	– 17

this loss amounts to about 8%–10% and is statistically significant (Haug 1984 b).

At the same time, our results demonstrate that the onset of brain volume loss is highly divergent. For instance, one can find extremely high brain weights in very old individuals. This means that the onset and rate of aging events in the human brain differ widely from individual to individual.

Aging of Various Brain Regions

With the help of new morphometric procedures, we (Eggers et al. 1984) have measured the gray and white matter in different regions of the brain. Our results are expressed in percentages on account of the large discrepancies in brain size. Calculations of whole brain size were based on our estimates of the effects of secular acceleration.

Table 1 summarizes the most important results. The entire brain of a 75-year-old is, on the average, about 6% lighter than that of the average 25-year-old. However, the 15% decrease in the weight of the frontal cortex (in front of the motor area) is not proportional. On the other hand, the regions involving sensory and speech functions in the parietal and occipital lobes do not change in size. A larger loss of volume during aging can be found in the central ganglia (thalamus and corpus striatum). White matter also decreases in size.

To summarize, the various regions of the brain undergo different macroscopic alterations during aging. This also applies to the cerebral cortex, where the frontal cortex undergoes marked shrinkage during aging, whereas the parieto-occipital cortex does not change in size.

Effects of Aging on the Neurons of the Cerebral Cortex

Morphometric assessments of the number and size of neurons in the aging cortex must take into account the variability within a population. Figures 3 and 4 show the variability in neuron density and size. Our estimates are based on measure-

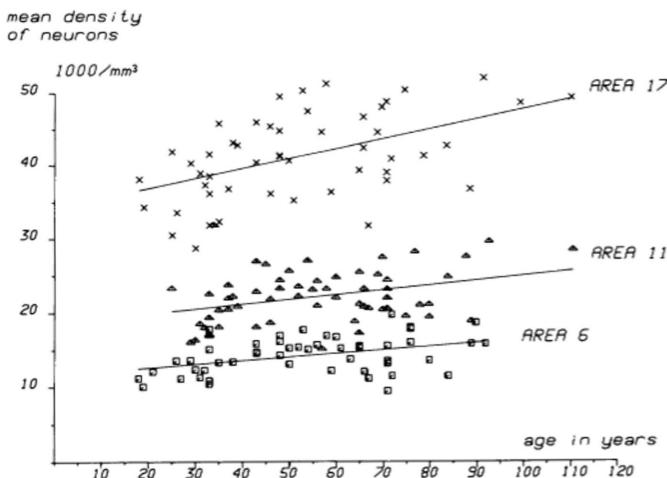


Fig. 3. Mean neuron density in areas 6, 11, and 17, expressed in $1,000/\text{mm}^3$ (*ordinate*). In spite of marked individual variability, the significance of the age-related increase in density for area 17 (visual cortex) is high ($P=0.001$). In areas 6 and 11, the significance of this increase is $P=0.01$, while in areas 7 and 20, the variability is insignificant

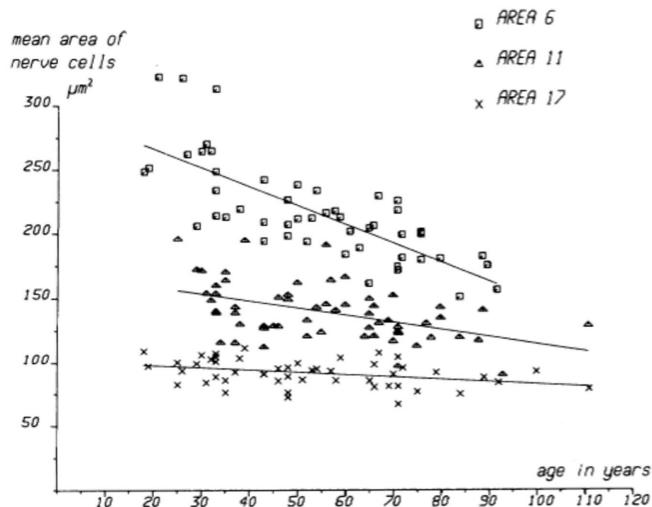


Fig. 4. Mean size of perikarya in brain areas 6, 11, and 17, expressed as the projection area in μm^2 (*ordinate*). The decrease in size is highly significant, ($P=0.001$) for areas 6 and 11, significant ($P=0.05$) for area 17, barely significant ($P=0.1$) for area 20, and insignificant for area 7

ments of at least 50 brains in each area, except for area 20 of the temporal cortex, for which measurements of only 20 brains are provided.

All cases with pathologic or psychologic alterations were eliminated from our study in order to focus on biological aspects of aging. A surprising observation was that neuron density does not diminish during aging, after allowing for embedding shrinkage (Fig. 1). All the results of the microscopic morphometry dis-

cussed here are based on fresh or unfixed human brain. Therefore, the neuron densities represent the actual number of neurons in living brain tissue for the brain areas examined (Haug 1984a; Haug et al. 1983; Haug et al. 1984).

It is striking that, with age, some areas show an increase in neuron density per mm^3 . This is primarily true of area 6 (extrapyramidal cortex). On the other hand, we found that macroscopically speaking, this area decreases in size. The increase in density is probably connected with this decrease in volume. This question is discussed further.

Figure 3 compares the neuron density of three of the five evaluated areas. Areas 7 and 20, which are not shown here, show the same tendencies as area 11. An increase in neuron density with age can be observed in all areas except areas 7 and 20.

Perikaryon size shows different tendencies. Figure 4 demonstrates the changes in neuron size for three brain areas. Area 6 exhibits a striking degree of diminution of neuron size with age. Area 17 shows a lower, though still statistically significant reduction in size, while area 7 shows little diminution of neuron size.

A first glance at area 11 (psychosocial functions) reveals similarities to area 6. However, the decrease in neuron size does not occur continuously. Figure 5 demonstrates this by illustrating the reduction in cell size occurring with age. Cell area remains constant up to age with a slight increase possible around age 50. After 60 years of age, mean size shrinks noticeably. We feel that our results are valid, in view of the fact that 70,000 neurons were examined.

As far as neuron density and size are concerned, area 20 shows a pattern similar to that of area 11, despite the fact that only 20 brains were studied. It is probable that the neurons in this area also diminish in size after 60 years of age.

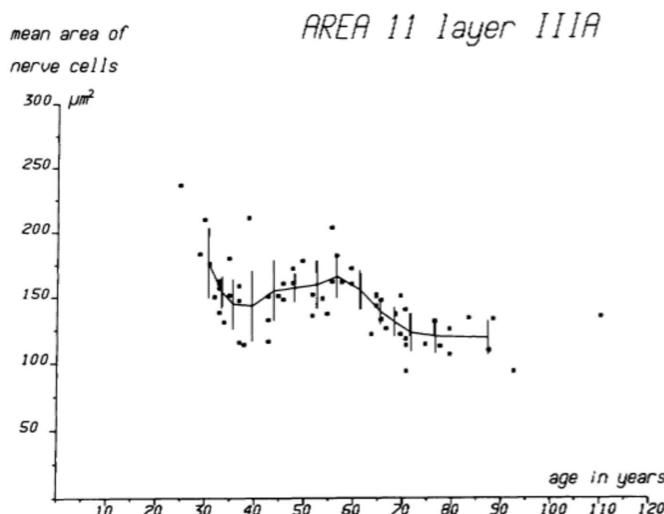


Fig. 5. Mean size of perikarya in a typical layer (layer IIIa) of area 11, as expressed by an empirical regression (Peil and Schmerling). The graph demonstrates that neuronal shrinkage can be clearly observed only after 60 years of age. The tendency toward an increase in area from age 50–60 is not significant

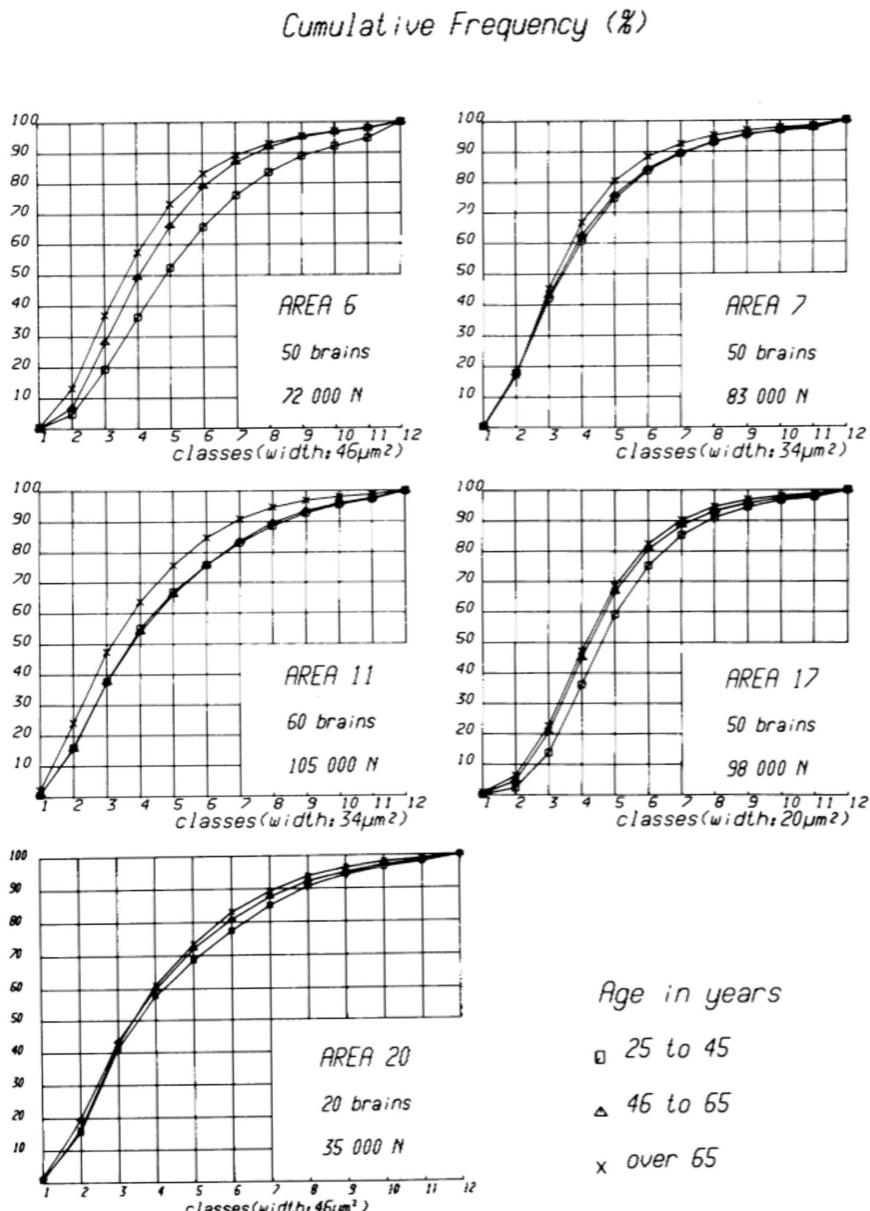


Fig. 6. Size distribution of cortical neurons in five human cortical areas shown for three age groups. Curves represent cumulative frequencies beginning with the smallest cell class. The cell classes differ according to the size of the neurons in each brain area. Curves at the left represent small neuron distributions and, at the right, larger size distributions

The higher parietal cortex (area 7) and the visual cortex (area 17) reveal decreases in nerve cell size that remain relatively small until old age, with a shrinkage amounting to about 10% in volume. Area 6 undergoes a mean volume decrease of 30%–35%, while areas 11 and 20 are diminished by between 10% and 30%.

Figures 4 and 5 do not demonstrate how the different neuron sizes contribute toward the overall reduction in mean projection area. This is illustrated with the size distribution graphs in Fig. 6. The five graphs show the overall neuronal size distribution for 12 size classes expressed in curves of sum frequencies. Such curves can answer further questions concerning the degree and rate of age changes for different sizes of neurons. The total number of cells analyzed for each curve corresponds to 100%.

The scales of the cortical areas studied vary as to the arrangement of size distribution according to differences in mean neuronal size. Steep sections of the curves indicate that the corresponding size classes contain many cells, while flat sections describe classes with few cells. The curves in one graph depict three age groups. The curves lying more to the right are based on larger cell size distributions and, vice versa, the curves at the left are based on smaller ones. The distance between the curves expresses the difference in size between the projection area of neuronal sizes for the various age groups.

The large distance separating the age curves for area 6 means that cell size diminishes continuously for all size classes in the three age groups. The curves for area 7 show that only a very small decrease in cell size takes place during the aging process. Area 11 exemplifies yet another pattern. Cell size remains nearly unchanged up to age 65, after which a distinct decrease in size can be observed. This accords with the distribution of mean sizes shown in Fig. 5. The visual cortex, with its relatively small cells, shows a slight, but continuous decrease in cell size with age.

The graphs in Fig. 6 demonstrate that the decreases in size undergone by cells in one area of the brain during aging are similar. After evaluating 20 brains, we believe that area 20 of the temporal cortex shows aging patterns similar to those seen in area 11 (Nass 1985).

Similar observations regarding neuron size have been made by Uemura and Hartmann (1978). Our own examinations involve the various layers of the cerebral cortex. Though some smaller discrepancies can be observed, they have no implications for our view of the aging process.

Total Number of Neurons in the Human Cerebral Cortex

The neuron density and cortical volume of which it was possible to calculate from individual brain weights allow an estimation of the total number of neurons in the whole cortex. Cortical volume, in turn, amounts to about 47.5% of the total brain (Schlenska 1969; Haug 1970; Eggers et al. 1984).

Figure 7 shows that the number of neurons varies considerably. It should be noted here that Fig. 7 records only those brains for which values based on two or more areas were available. The mean number of neurons in the human cerebral cortex totals 13.9×10^9 (billions), with a range of between 10 and 20×10^9

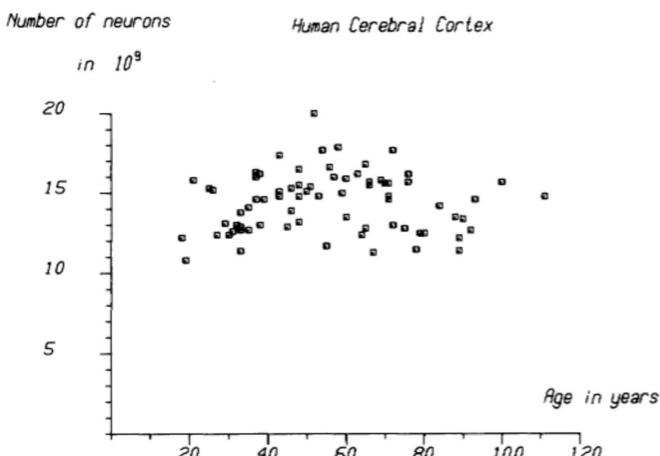


Fig. 7. Total number (in billions) of neurons in the entire human cerebral cortex (*ordinate*). Each mean value contains values for at least two areas. The values are calculated according to normalized mean density; the weight of cerebral cortex represents 47.5% of the average whole brain. Total number of neurons does not appear to change with age

neurons. We cannot discern any tendency for the number of neurons to diminish with age, but it must be noted that the decrease in brain size is counterbalanced by an increase in neuron density (Fig. 3).

In summary, the following statement is possible: the total number of neurons in the human cerebral cortex does not change during the aging process, if all pathologic material is excluded from consideration. However, this result is not representative of brain regions other than the cortex. Furthermore, it is probable that pathologic material reveals degeneration, as for example, in Alzheimer's disease (Terry 1983).

Aging of Cortical Ultrastructures

The analysis of the ultrastructure covers the entire neuron, including the perikaryon, dendrites, neurites, synapses, and glia with processes and vessels, and implements high-power images, usually produced by electron microscopy. Methodologically the morphometry of these structures has not yet been satisfactorily resolved. Two procedures are important. However, because of the effort involved, they have not been used very frequently:

1. The neurons and their processes can be stained by Golgi staining with silver. In conjunction with light microscopy, this stain reveals that the larger dendrites have spines representing a kind of synaptic contact from neuron to neuron. It is possible to count this type of synapse. Marin-Padilla and Marin-Padilla (1982), Scheibel and Scheibel (1978), Schierhorn (1978), and Schönheit and Schulz (1978) have shown that the number of spines decreases with age, bringing about a concomitant decrease in the numbers of synaptic contacts.

Some investigations suggest that the reduction in synaptic contacts is accompanied by a decrease in functional ability (see below). However, it should be mentioned that at present little research on this issue has been done.

2. Contrary to the autolysis of other ultrastructural components, it is possible to stain the synapses in the human brain for electron microscopy with a phosphotungstic procedure. Huttenlocher (1979) has found out that the density of synapses decreases slightly with age. With this procedure, it is possible to examine more types of synapses than with light microscopy, which reveals only spine synapses.

Such examinations should be increasingly used in the future, on the grounds that the slight aging changes discovered by light microscopy force us to look more closely for age changes at the ultrastructural level, especially those involving synapses, neuronal processes, and vessel walls.

Uemura and Hartmann (1978) and Higatsberger et al. (1982) report a loss of DNA and other neurochemical substances in the nerve cell bodies of human brain. Carlsson (1981) found a slight decrease in neurotransmitter levels, which are sometimes diminished at an increasing rate after 60 years of age.

Aging and the Human Brain: New Insights

These and other developments have led to new insights in our understanding of morphological and functional changes taking place in the human brain during the aging process:

1. Morphometric results of macroscopy and light microscopy show that, up to 60–65 years of age, no or only small changes occurring as a result of aging can be observed in the human cerebral cortex with the exception of area 6, see point 2. It should be pointed out that this is a statement of statistical probability, meaning that, on an average, the onset of morphological age changes in the human cortex may be expected to occur around age 60–65. However, on an individual basis, the age at which such alterations may occur varies. The time of onset and speed of aging probably depend on a genetic program.
2. Aging differs in time, extent, and rate for the gray matter of different regions. Aging changes in area 6 of the human cortex begin very early (Between the ages of 25 and 40 years). Those taking place in the visual cortex (area 17) and the parietal lobe (area 7), which play a role in sensory processes, begin late in life, as revealed by macroscopic and microscopic morphometric examinations. Psychosocial functions regulated by the orbital part of the frontal lobe (area 11) exhibit special traits. Neuron measurements do not show changes until retirement age. After the age of 65, pericaryon size diminishes noticeably.
3. At present, the effects of aging changes in the ultrastructure of the human cortex are too slight to have been convincingly demonstrated. However, preliminary examinations suggest that the density of synapses decreases with advancing age, though details of how this occurs remain unknown (see point 4). It is

to be hoped that more studies using ultrastructural techniques will broaden our knowledge in this field.

4. Experiments with aged rats have shown that environment exerts a strong influence on the aging process (Connor et al. 1981, 1982; Diamond and Connor 1982). Rats identical in age were housed in a narrow cage comparable to the restrictive environment of a home for the elderly. After a certain amount of time had elapsed, they showed a considerable loss of spine synapses in the cerebral cortex. On the other hand, rats of similar age and breeding which are put into large cages with an enriched environment together with rats of other ages reveal no loss of spine synapses after the same period of observation. This finding suggests the following conclusion: the use of cortical neuronal connections permits conservation of these structures and their functions. This is not a new statement, as it is well-established, for example, that muscles which are not used undergo atrophy.
5. It is well-known in human psychology that work and activity help to conserve mental ability, while an impoverished environment (like certain inferior homes for the elderly), by imposing a life of relative inactivity, leads to atrophy of brain structures.
6. Our own results demonstrate that the extrapyramidal human cortex (area 6) begins to age relatively early, as a result of a decrease in motor activity. On the other hand, the sense organs continue to be used, even in old age or in an environment of poor quality, which permits long maintenance of structure and function. With such findings in mind, we can more easily grasp the observations regarding area 11 in the basal frontal cortex, which are related to psychosocial functions. Cortical structures are preserved until retirement age. After retirement, the need for preservation diminishes and, consequently, one can begin to observe changes in the cortical structure.
7. The genetically determined timetable of age changes occurring in various parts of the cerebral cortex is slowed or accelerated, depending on the degree to which brain functions are put to use. With this in mind, we can understand why individuals who work beyond the normal retirement age retain their mental faculties into old age. Political leaders in a number of countries are examples of this.
8. Some studies have shown that metabolic changes also occur during aging (Ulffert et al. 1982; Sarkander et al. 1982).

The current discussion in the Federal Republic of Germany regarding the appropriate age for retirement shows little concern for the aged. However, the individual's own experience and the observations of science make us realize that the normal working life should be extended. In the USA, some changes have been brought about as a consequence of this viewpoint. The enormous changes taking place in the workplace compel us to find new solutions concerning the length of our working life. I think retirement age should be very flexible, so that it can be adapted to the capabilities of the individual. Furthermore, it should not be forgotten, that, in a few years, the age groups beginning their working life will be very small, according to demographers. This will probably lead to the extension of the normal working life, because the problem of financing retirement pensions will provide additional incentives for a longer working life.

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