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Different developmental rates of selected brain structures in humans

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Abstract. Various rates of development are characteristic for particular structures of the human central nervous system (CNS). The differences of the maturing brain stem and telencephalon are evident in a routine neuropathological examination. The fetal and postnatal archi- and neocortex also reveals uneven levels of maturation. In order to precisely describe those differences in humans we performed a morphological and morphometric study on the dorsal vagal nucleus of the medulla oblongata, on Ammon's horn and on neocortex from midgestation to the 18th postnatal month. The numerical density of neurones, cell perikarya and nuclear cross-sectional area, and the ratio of nucleus to perikaryon area were measured. The results demonstrate a development-dependent decrease in cell density and progressive differentiation of neurones according to their changing size. They express a process of maturation which differs in rate across the CNS structures examined.

Key words: human brain development, dorsal vagal nucleus, hippocampus, temporal cortex, morphometry

INTRODUCTION

The central nervous system (CNS) in humans is a complex organ arising as a final result of philogenetic and ontogenetic development. The parallels between them remain until now a question. Differences in developmental rates between older and younger structures are well seen in gross morphology of developing brain at its early stages. It is known that such differences have evident implications for appearance of early arising cerebral dysgeneses, but the uneven rate of further maturation of brain structures may also play a role in the course of pathological processes starting at that time. Therefore it seemed interesting for us to compare the parameters of neuronal maturation within structures developing at different rates: the brain stem, the hippocampal cortex and the neocortex, using quantitative histologic methods.

The brain stem undergoes basic developmental processes during the second month of gestation, and at the end of the 7th week of gestation (WG) the "principal neuronal system" for rhombencephalic reflexes "is on definitive position" (Sidman and Rakic 1982). Among the structures of the brain stem the dorsal motor vagal nucleus (DVN) has been chosen for our study.

The hippocampus, traditionally classified as archicortex, arises early. The primordium of the hippocampus is seen at 4.5 WG on the cortical plate (Muller and O'Rahilly 1988). During the 10th to 12th WG migration of cells from the ventricular zone to the archicortex is very rapid, and morphological changes in neuronal differentiation within the hippocampus appear at 13-14 WG (Sidman and Rakic 1982). We decided to examine maturation of CA1, CA2, CA3 and CA4 sectors of Ammon's horn (hippocampus proper), which are well distinguishable after midgestation, in order to estimate quantitatively the observation of Filimonoff (1964) that histogenesis in the archicortex starts later than in the neocortex, but neurones mature earlier.

Neocortical development starts early. Migration of neurones to the cortical plate begins before the end of the 2nd month, its active period continues until the end of the 5th month, but is prolonged beyond birth (Sidman and Rakic 1973, Choi 1988). We decided to examine the maturation of neurones from the inferotemporal (IT) cortex for comparison with hippocampal cortex. The period between the second half of gestation until the 18th month after birth seemed to be most suitable for examination because of intensive brain maturation at that time.

METHODS

The brains of 15 human subjects of both males and females ranging between 20 WG to 18 month (M) after birth were used. There was no history of neurological diseases. The brains were weighed and fixed in 10% formalin for 2-4 weeks. Paraffin-embedded slides from representative brain regions were routinely processed for histological examination. In all cases, neuropathological investigation did not reveal any abnormalities except for cerebral hyperaemia and recent intraventricular hemorrhage in two cases (22 and 28 WG). In cases obtained at 20 WG (one case), 22 WG (one case), 40 WG - full term newborn (three cases) and 11 M (one case) the

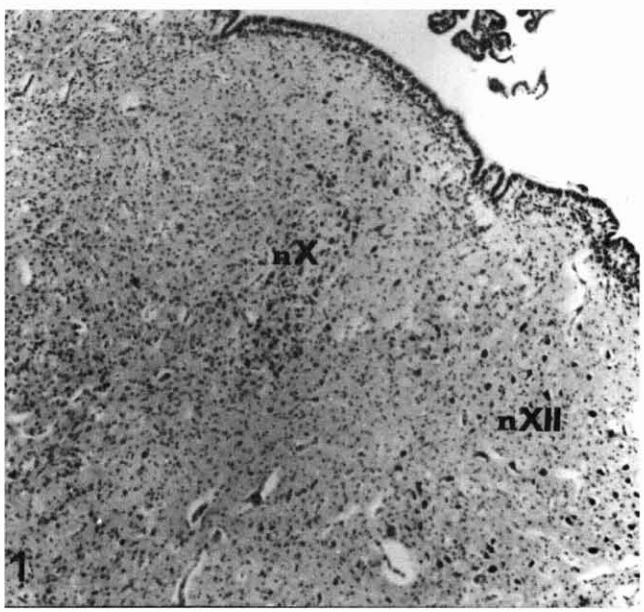

Fig. 1. The medulla oblongata at the intermediate part of the DVN in the human fetus at 40 weeks gestation. nX, dorsal motor nucleus of the vagus nerve; nXII, hypoglossal nucleus. Cresyl violet x 40.

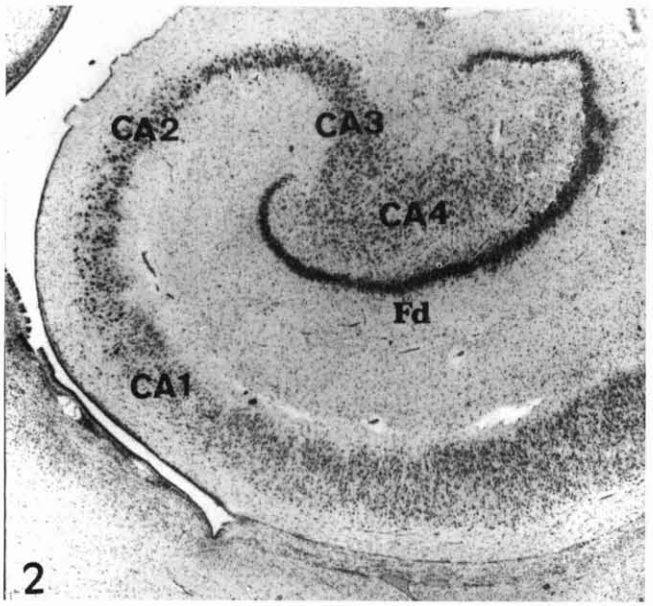

Fig. 2. The hippocampus at the level of lateral geniculate body in the human fetus at 40 weeks gestation. CA1, CA2, CA3, CA4 sectors of the Ammon's horn. Fd, Fascia dentata. Cresyl violet x 20.

mid-level of the medulla oblongata was serial cut and every 50th coronal section (10 μm thick) was selected, taking into account the number and diversity of neurones in the DVN. In cases obtained at 28 WG (one case), 32 WG (two cases), 40 WG (four cases), 11 M (one case) and 18 M (one case), from the left temporal lobe including the middle part of the hippocampus and the inferior temporal gyrus, a single 8 μm coronal section was taken. Neuronal development was evaluated in the DVN (Fig. 1), in four hippocampal sectors: CA1-CA4 (Fig. 2) and in layer III and V of the IT cortex (Fig. 3). The location of the DVN (left nucleus) was delineated according to Olszewski and Baxter (1954). The hippocampus was divided into CA1 through CA4 according to Lorente de No (1934) and Duvernoy (1988). The area of the IT cortex examined in this study was taken from the crown of the inferior temporal gyrus. The measurements were performed on sections stained with cresyl violet. One hundred randomly selected neurones from each structure were examined. The neurones and their nuclei were traced at a magnification x 1,600 using a projection microscope (Pictoval, Carl Zeiss Jena). Only the pyramidal cells of temporal cortex from fetuses at 28-32 WG of age were outlined at x 3,200; because of their immaturity and very scarce cytoplasm they were difficult to recognize at lower magnification. Cross-sectional perikaryon and nuclear areas (in μm^2), and ratio of nuclear to perikaryon area given in percent were calculated with the use of a morphometric program (Sigma-Scan, Jandel Scientific Corp. USA) installed on a computer connected to a digitizer (Summagraphics MM 1201). Neurones in the examined structures were classified according to the profile area of the cell bodies into subpopulations. Cell density measurements were made in the DVN and the hippocampal CA1-CA4 sectors using the same coronal sections as were used for analysis of cell size. The number of neurones containing a nucleus was determined within test fields

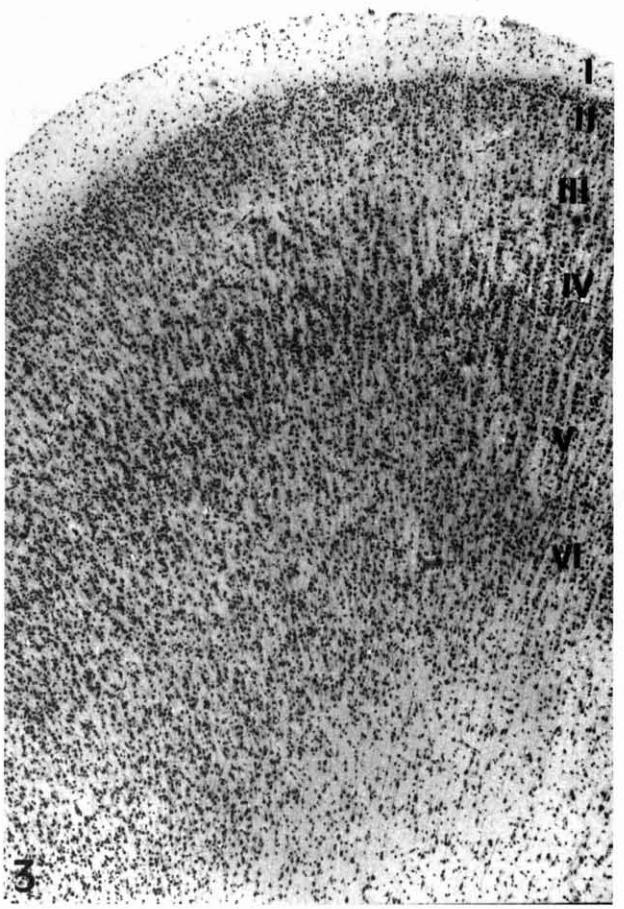

Fig. 3. The cytoarchitecture of the IT cortex in the human fetus at 40 weeks gestation. Cresyl violet x 40.

corresponding to the entire surface of the structure accessible on examined sections at x 540 with a projection microscope. The area of test fields was calculated, and the neuronal densities were expressed as the number of cells beneath one square millimeter of the DVN or the hippocampal pyramidal layer surface.

RESULTS

Neuronal size

The DVN demonstrates at midgestation a rather large mean profile area of neuronal bodies, and their growth is more accentuated before than after birth (Table I). Nevertheless, this process continues until the end of the examined period. Although the neuronal population of adult DVN includes neurones of various size and shape (Huang et al. 1993), the relationship between them changes during development. The distribution of neuronal areas of the DVN at various ages is shown in Fig. 4. At 20-22 WG very small neurones up to 40 μm^2 were seen, together with those of 200-250 μm^2 profile area. At birth neurones of medium size (120-200 μm^2) dominated, but larger neurones up to 350 μm^2 of profile area were seen. This trend in development continues after birth. This process is illustrated by the morphological pictures (Fig. 5A, B and C).

The four sectors of Ammon's horn, beginning at 28 WG when it is possible to recognize even less

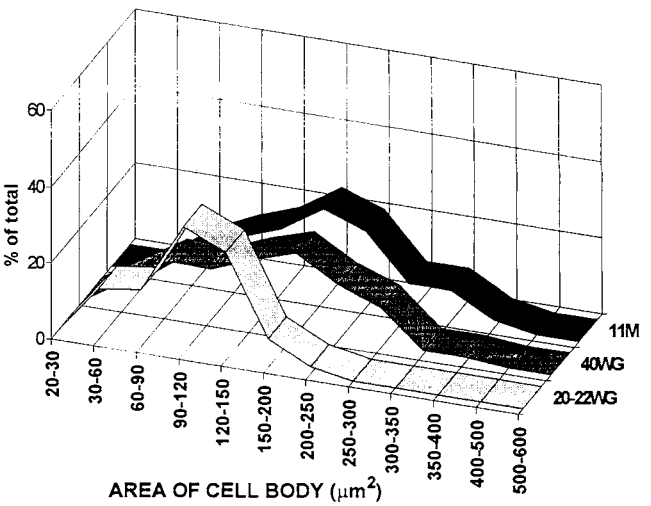

Fig. 4. Histogram of the distribution of cross-sectional area of DVN neurones during pre- and postnatal development. WG, gestational age in weeks; M, postnatal age in months.

mature neurones, demonstrate differences in neuronal maturation (Table II). It is well evident that the CA2 sector is the most mature among all sectors, while CA1 and CA4 sectors are the least mature ones. In all sectors, mainly in CA2 and less intensively in CA1, the mean profile area of cell bodies gradually increases until birth. This process becomes more accentuated after birth, and at 18 M of age even the small neurones of CA1 sector (mean 56 μm^2) reach the parameters of large ones (mean 250 μm^2) and CA2 sector is characterized in particular by very large cells (mean 380 μm^2). The

TABLE I

Morphometric values of neurones in the DVN from midgestation until postnatal age

Age	The perikaryon cell area (μm^2)	The nuclear cell area (μm^2)	Nuclear to perikaryon area ratio (%)
20WG	114.3±2.5	49.5±1.2	43.6±0.7
22WG	100.6±4.5	44.4±1.9	45.2±0.8
40WG	157.7±4.3	70.2±1.4	48.1±0.6
11M	184.5±7.3	102.5±3.4	57.5±0.9

WG, gestational age in weeks; M, postnatal age in months. Values are expressed as mean ±SEM of the pooled individual results.

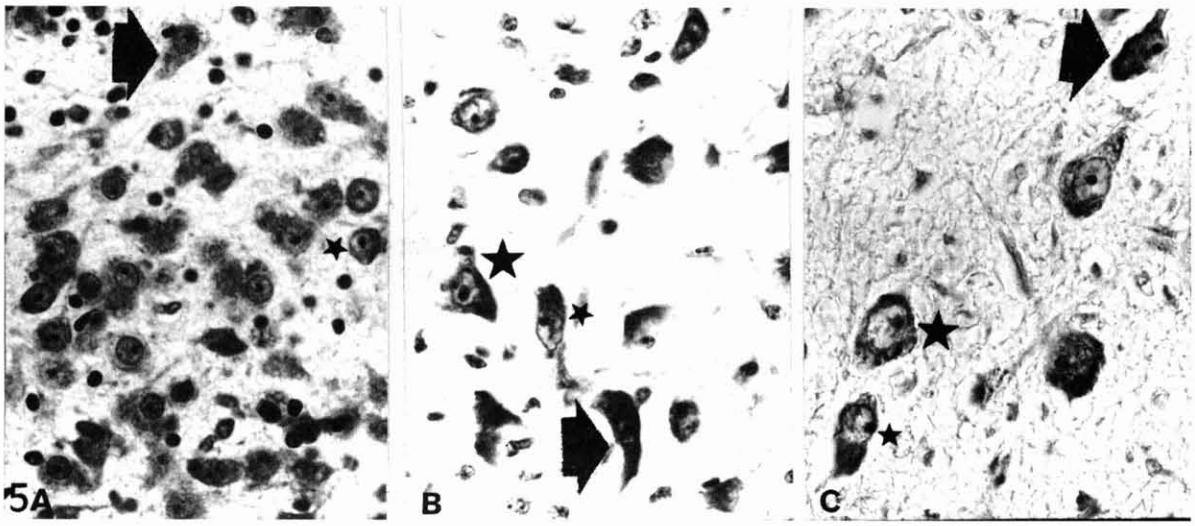

Fig. 5. Neuronal maturation in the DVN. A, 20-week human fetus. B, 40-week human fetus. C, 11 months postnatal. Note various cell types: fusiform (arrow), ovoid (small asterisk) or multipolar (large asterisk). Cresyl violet x 400.

histograms of distribution of neuronal areas in Ammon's horn allow a better insight into the neuronal populations of these sectors. In CA1 (Fig. 6A) from 28 WG to 40 WG the neuronal areas are distributed between 30-120 μm^2 and 30-150 μm^2 of profile area, respectively, but later, at 18 M of post-

TABLE II

Morphometric values of neurones in CA1-CA4 sectors of the hippocampal cortex from midgestation until postnatal age

Age	CA1	CA2	CA3	CA4
The perikaryon cell area (μm^2)				
28WG	56.2±1.2	127.5±2.8	89.1±2.0	59.8±1.9
32WG	74.8±0.8	160.0±2.8	112.9±1.8	71.5±1.2
40WG	71.8±0.8	174.7±2.5	130.6±1.6	96.1±1.4
18M	251.6±3.6	380.4±8.6	275.7±5.9	294.0±6.8
The nuclear cell area (μm^2)				
28WG	35.3±0.8	66.6±1.5	48.1±1.0	34.0 ±1.0
32WG	47.5±1.2	79.9±1.1	55.8±0.8	41.4±0.9
40WG	45.7±0.4	75.0±0.8	67.0±0.7	50.9±0.6
18M	116.9±1.1	145.2±1.9	112.9±1.7	122.6±2.2
Nuclear to perikaryon area ratio (%)				
28WG	63.7±1.1	52.7±0.7	54.7±0.9	58.1±1.0
32WG	63.4±1.5	53.2±1.1	51.8±1.0	57.8±0.9
40WG	64.6±0.3	44.8±0.4	52.1±0.3	53.8±0.3
18M	47.1±0.6	39.7±0.8	41.9±0.6	42.8±0.6

WG, gestational age in weeks; M, postnatal age in months. Values are expressed as mean ±SEM of the pooled individual results.

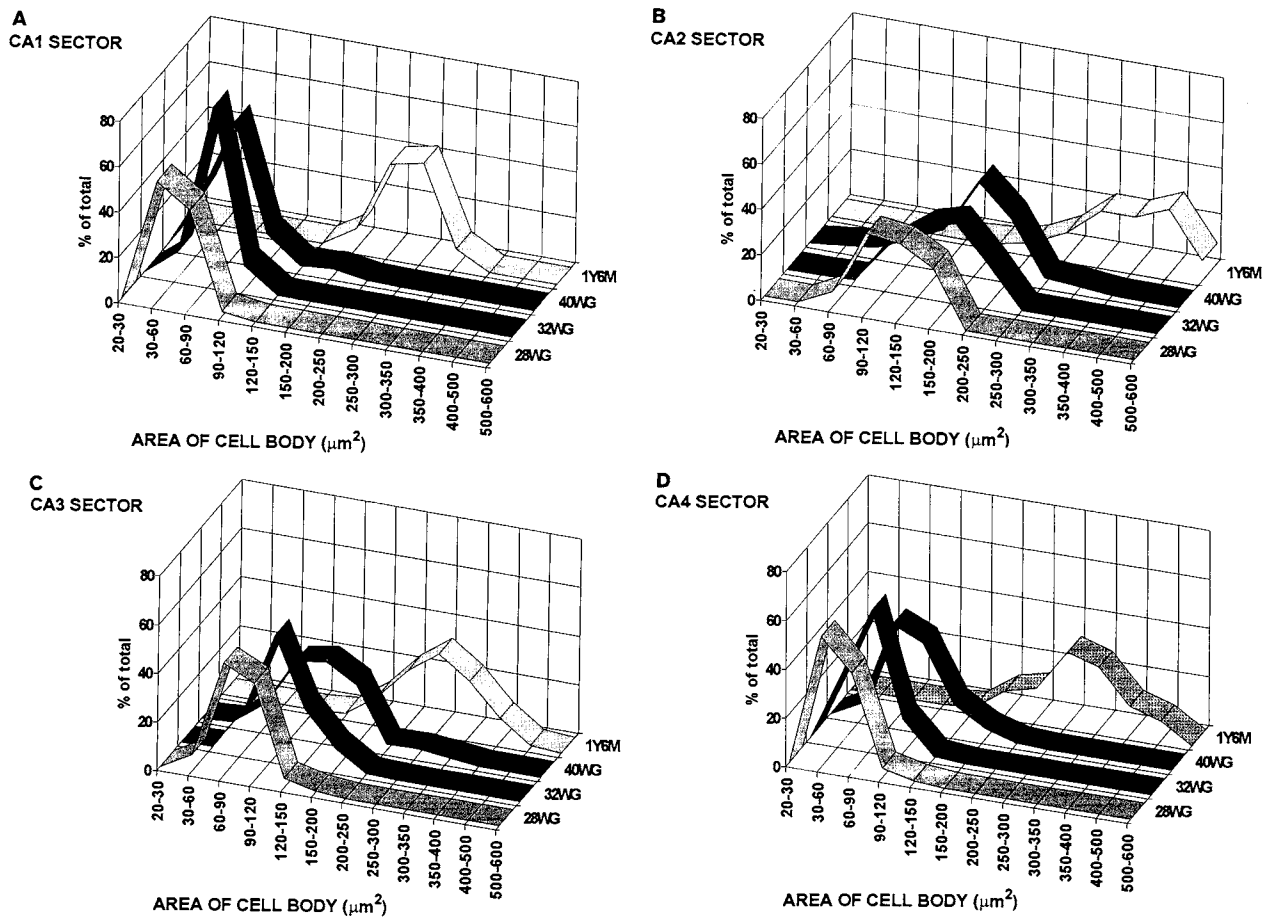

Fig. 6. Histograms of the distribution of cross-sectional area of the pyramidal cells in the middle part of the hippocampus in sector CA1 (A), CA2 (B), CA3 (C), CA4 (D), during pre- and postnatal development. WG, gestational age in weeks; Y, M, postnatal age in year, months.

natal age, the larger ones start to predominate and the smallest exceed 150 μm^2 of area. In CA2 (Fig. 6B) from 28 to 32 WG the neuronal areas are distributed between 60-150 μm^2 and 60-250 μm^2 of profile area, respectively. Around birth an increase in the number of larger cells up to 250 μm^2 of profile area is seen. At 18 M of age the neuronal areas are distributed between 150-600 μm^2 but very large ones between 300-500 μm^2 of area dominate. The CA3 and CA4 sectors present similar rates of development (Fig. 6C and D). From 28 to 40 WG the neuronal areas are distributed between 30-250 μm^2 of profile area. In CA3 and CA4 sectors, the small neurones (to 120 μm^2 and 90 μm^2 of area, respectively) dominate at 28 WG and medium ones (90-200 μm^2) at 40 WG. Development progresses postnatally, and at 18 M of age large neurones (over 200 μm^2) in CA3 and even very large (up to 300 μm^2 of area) in CA4 dominate. Despite advancing maturation of all sectors this process is most accentuated in CA2, which was more mature than all others during the whole observation period. The morphological pictures present well the results of uneven maturation of Ammon's horn sectors (Fig. 7A-F).

Among all the examined areas the IT cortex, which is six layered neocortex, is most immature. At 28-32 WG when most cells were very small we examined only neurones clearly distinguished from glia. In both layers III and V, the mean profile area of neurones gradually increases during gestation, but the most intensive development occurs after birth (Table III). Nevertheless, until 18 M of age the

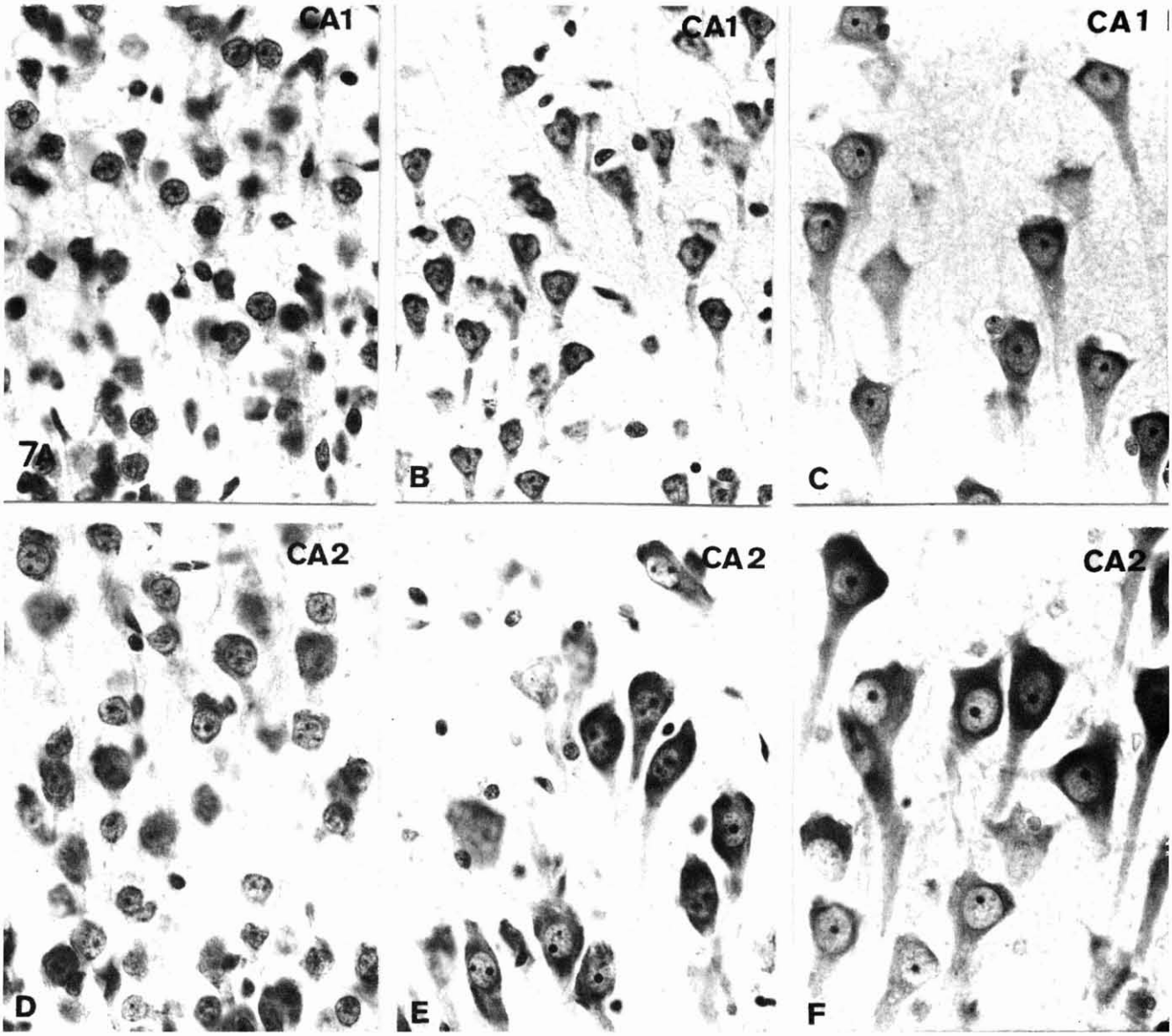

Fig. 7. Maturation of the hippocampal pyramidal cells in CA1 and CA2 sectors. A and D, 28-week fetus; B and E, 40-week fetus; C and F, 18 months postnatal. Cresyl violet x 400.

mean area of cell bodies is less than 200 μm^2. The distribution of neurones according to their size is similar in both layers (Fig. 8A and B). In the youngest specimens small and even very small neurones (20-60 μm^2) dominate, and the prevalence of medium sized neurones and appearance of large ones occurs between 11-18 M of age. The morphological pictures illustrate the process of neuronal maturation (Fig. 9A, B and C).

Nuclear to perikaryon area ratio

Another parameter illustrating the maturation of neurones is the evolution of the mean nuclear/perikaryon area ratio, expressed in percent of cell area occupied by the nucleus.

In the DVN (Table I) this ratio is rather low at 20-22 WG and increases slowly. This reflects the parallel growth and maturation of both components.

TABLE III

Morphometric values of neurones in temporal cortex of layer III and layer V from midgestation until postnatal ages

Age	Layer III	Layer V
The perikaryon cell area (μm^2)		
28WG	45.4±1.0	47.8±1.1
32WG	54.2±1.5	59.5±1.5
40WG	82.7±1.0	82.7±1.4
11M	150.6±3.7	148.0±4.1
18M	180.8±4.9	170.6±5.3
The nuclear cell area (μm^2)		
28WG	37.2±0.8	41.0±0.9
32WG	43.0±1.4	48.6±1.3
40WG	54.8±0.5	51.9±0.6
11M	75.8±1.3	76.1±1.6
18M	93.6±2.0	104.4±2.8
Nuclear to perikaryon area ratio (%)		
28WG	82.2±0.8	86.1±0.6
32WG	79.0±1.2	81.5±1.0
40WG	67.7±0.4	64.5±0.4
11M	51.5±0.6	52.8±0.8
18M	53.0±0.8	62.6±1.0

WG; gestational age in weeks, M; postnatal age in months. Values are expressed as mean±SEM of the pooled individual results.

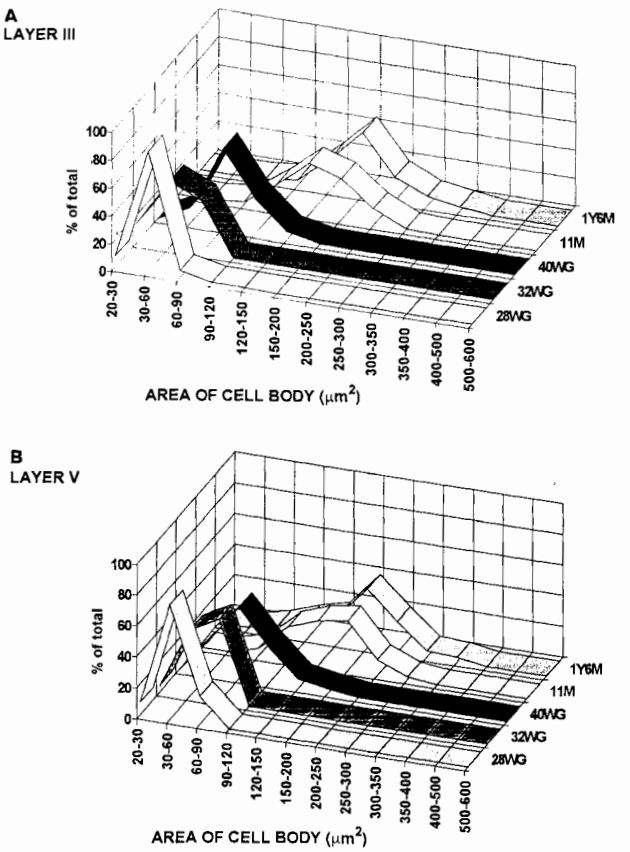

Fig. 8. Histograms of the distribution of cross-sectional area of neurones in layer III (A) and V (B) of the IT cortex during pre- and postnatal development. WG, gestational age in weeks; M, Y, postnatal age in months, year.

In Ammon's horn (Table II) this parameter between 28-40 WG is higher in CA1 where the cytoplasm is scarce, and is the lowest in CA2 which has more mature cells. In CA2 a rapid decrease of the ratio during the prenatal period indicates much more growth of perikaryon than nucleus. In CA1 this process is most accentuated after birth. In CA3 and CA4 the process is similar to that seen in CA1.

In the IT cortex (Table III) the nuclear to perikaryon area ratio is particularly high at 28 WG when the cytoplasm is extremely scarce, and decreases until about 1 year of age. Between 11-18 M of age when the growth of nucleus and cytoplasm becomes more parallel the ratio increases.

Density of neurones

As a final parameter we studied the density of neurones per mm^2 in the DVN and in Ammon's horn. Because the IT cortex is most immature at 28-32 WG and it is difficult to differentiate all neurones from glial cells during examination with a light microscope, we did not include this structure in the estimation of neuronal density.

In the DVN neuronal density decreases rapidly between 20-22 WG and gradually from midgestation to 11 M after birth (Fig. 10). Neuronal density in Ammon's horn is much higher prenatally (from 28 to 32 WG) in CA1-CA3 sectors than postnatally (Fig. 11). At 40 WG a marked decrease in neuronal density appears in CA2 and CA3 sectors. In CA1 the density of neurones remains higher than in other

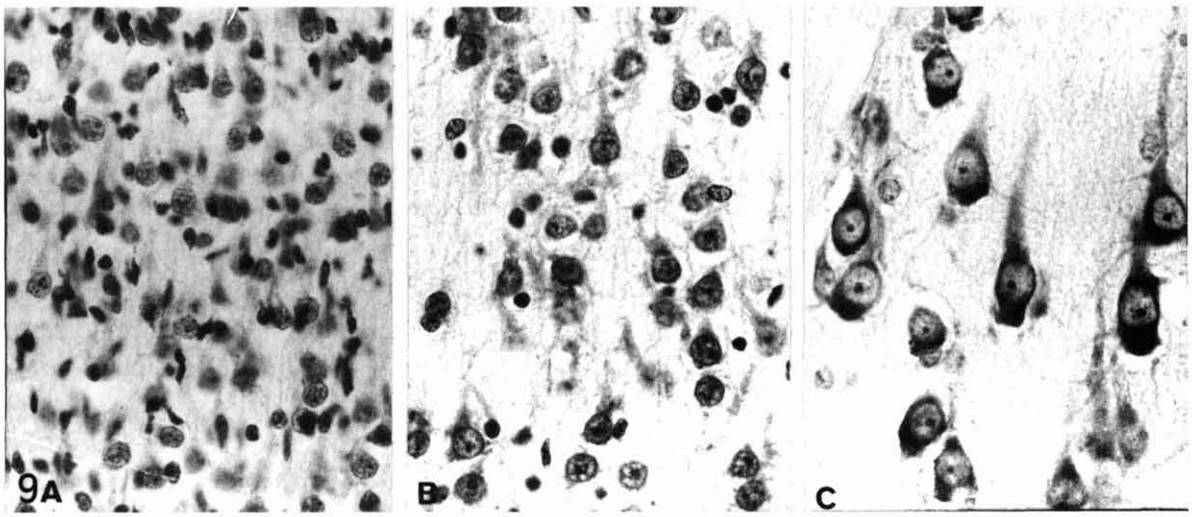

Fig. 9. Neuronal maturation in layer III of the IT cortex. A, 28-week fetus; B, 40-week fetus; C, 18 months postnatal. Cresyl violet x 400.

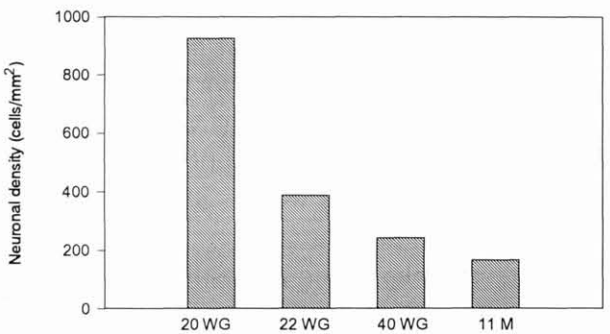

Fig. 10. Neuronal densities (cell/mm^2)in the DVN. WG, gestational age in weeks; M, postnatal age in months.

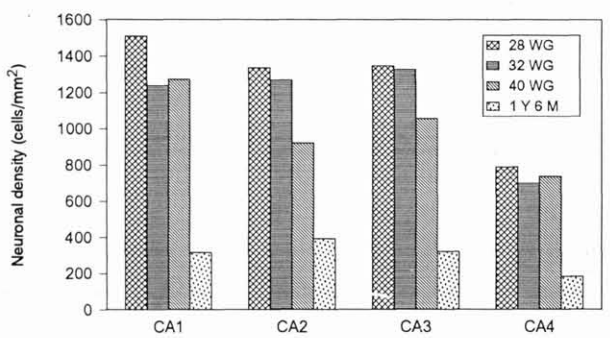

Fig. 11. Comparison of neuronal densities (cell/mm^2) in the hippocampal CA1-CA4 sectors. WG, gestational age in weeks; Y, M, postnatal age in year, months.

sectors. Postnatally, up to 18 M, neuronal density decreases markedly in CA1-CA4 sectors.

DISCUSSION

The results presented above allow us to evaluate quantitatively differences in maturation rates of the examined structures. The brain stem in humans matures with great intensity before birth in order to reach the level required for its activity in the independent life of a newborn. The DVN, which is part of the parasympathetic system, plays an important role in normal cardiorespiratory regulation (Olszewski and Baxter 1954). Therefore, research on DVN development may provide observations for analysing infant pathologic conditions with unknown etiology, but related to abnormalities in the neural control of the respiratory system, such as sudden infant death syndrome. The maturation of neurones in the DVN in our study was more accentuated before than after birth and its development appeared as more or less parallel with other structures within the brain stem. Prenatally, developmental changes in neuronal dendrites are slightly earlier in the reticular formation than in the DVN (Takashima and Becker 1986). Neuronal populations of the hypoglossal and the ventral cochlear nucleus show a rapid maturation after 32 WG and 18 WG, respectively (Nara et al. 1989, 1993).

In this study, it was demonstrated that the DVN is characterized by a linear increase in neuronal size during fetal development. It was in agreement with

the results obtained by Nara et al. (1991), as well as mean cell body area of neurones in similar age groups was almost comparable, despite application of embedding technique different than in our study. After birth until 11 M of age, as we present in a more detailed study (Dąmbska et al. in press), the developmental processes in the DVN continue progressively.

The development of the cortex starts later, but in Ammon's horn sector CA2 reaches an advanced level of maturation just at birth. This uneven maturation of CA1-CA4 sectors in newborns at term was described by Kuchna (1994). The actual data complete previous observations demonstrating that CA2 neurones are the most advanced in the developmental process during the whole period of pre- and postnatal maturation studied. The CA1 neurones particularly, but also CA4, are developmentally much younger, and in CA1 approach the rates of neocortical maturation. In fetuses from 28 to 40 WG, there was a gradual increase in the mean profile area of the hippocampal pyramidal cells. The relatively greater maturity of the neurones takes place during the postnatal period, mainly in CA1. Our data are in agreement with the concept that, during development, the size of neurones increases with decreasing density. The decline of neuronal density is due mainly to the growth of neuropil, including neuronal processes and their ramification, but also glial elements, vessels and myelin sheath. The estimation of neuronal density in sectors of Ammon's horn disclosed the greatest decrease in CA2 and CA3 sectors between 32 and 40 WG, and postnatally in CA1 and CA4 sectors. In the whole studied period of development we found the lowest neuronal density in CA4. One reason for the loose arrangement of neurones in CA4 may be related to the numerous dendrites and axons of the dentate granule cells (the mossy fibres) labelled using the Golgi method in the immature human hippocampus of fetuses and newborns (Seress and Mrzljak 1987). The analysis of pyramidal cell density from CA1 to CA4 revealed that the major decrease occurs postnatally. This corresponds to a volumetric study of developing hippocampal formation (Kretschmann et al. 1986), which showed that the largest increases in hippocampal volume occurred in the postnatal period. In the case studied at 18 M of age we found an adult-like level of neuronal density for all hippocampal sectors. In numerous morphometric investigations of pyramidal neurone density in adult human hippocampus (Ball 1977, Mouritzen Dam 1979, Mani et al. 1986, Kim et al. 1990, Davies et al. 1992) differing values were reported. Davies et al. (1992) in an analysis of these published studies provided some possible reasons, in particular that the part(s) or level of the hippocampus which were investigated may have had considerable influence upon the results. It was not unexpected in the current study to obtain some differences in hippocampal neuronal densities in the newborn as compared with previous examinations (Kuchna 1994) performed in the same age group but along the entire hippocampus, if neuronal density increases from anterior to posterior parts of the hippocampus (Ball 1977, Mouritzen Dam 1979). However, the trend of uneven maturation of CA1-CA4 sectors was supported as well as the measurement of perikaryon and nuclear area.

So far, morphometric investigations of the human developing brain structures are limited. Conel (1939, 1963) reported some data concerning cellular maturation in the cerebral cortex of newborns and infants but these data could not be compared with our results because of methodologic differences in hippocampal subdivision as well as in the counting procedure. The results from the IT cortex (layer III and V were chosen for quantitative study) showed gradually increasing size of neurones during gestation and the most intensive maturation after birth. The different groups of cells according to their size were similar in both layers. The sequence of cell maturation in layer III and V of the IT cortex was to a certain degree similar to that which was observed in CA1 sector of Ammon's horn. The hippocampus and the IT cortex play an important role in formation of memory function (Squire 1986, Zola-Morgan et al. 1982, Sass et al. 1990, Greenlee et al. 1993). The maturation process of these structures, intensively persisting during the first year of life, may participate in the response of

CNS activity to the development of interactions with the environment.

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