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Cell Loss in the Hippocampus of Schizophrenics

Peter Falkai[1] and Bernhard Bogerts[1]

[1]Medizinische Einrichtungen der Universität Düsseldorf, C. u. O. Vogt-Institut für Hirnforschung, Moorenstrasse 5, D-4000 Düsseldorf 1
[2]Rheinische Landesklinik, Psychiatrische Klinik der Universität Düsseldorf, Bergische Landstrasse 2, D-4000 Düsseldorf 12, Federal Republic of Germany

Summary. To investigate whether volume reduction of the hippocampal formation of schizophrenics, as described previously, is paralleled by loss of neurons and fibre systems, tissue volumes and cell numbers of all parts of the hippocampal formation in post mortem brains of 13 schizophrencis and 11 age-matched controls belonging to the Vogt collection were determined.

Volumes of the whole hippocampal formation ($P < 0.01$), the whole pyramidal band ($P < 0.001$) and the hippocampal segments CA1/CA2 ($P < 0.01$), CA3 ($P < 0.05$), CA4 ($P < 0.01$) were decreased, whereas no significant volume reduction of the alveus and fimbria hippocampi and prosubiculum/subiculum could be found. The perforant path showed a trend towards volume reduction ($P < 0.1$).

The absolute number of pyramidal cells (tissue volume × cell density) was diminished in CA1/CA2 ($P < 0.05$), CA3 ($P < 0.05$) and CA4 ($P < 0.05$), but was not significantly changed in the prosubiculum/subiculum, the presubiculum/parasubiculum and the granular cell layer of the dentate fascia.

Pyramidal cell loss in CA1/CA2, CA3, CA4 was more distinct in the paranoid patients than in catatonics. The findings are discussed with respect to current hypotheses of limbic dysfunction in schizophrenia.

Key words: Schizophrenia – Hippocampus – Neuropathology

Introduction

Recently, several well controlled morphometric studies of post mortem brains have demonstrated pathological alterations in limbic structures of the medial temporal lobe of schizophrenics. The main findings were altered orientation of hippocampal pyramidal cells (Scheibel and Kovelman 1984), reduced volumes of the hippocampus, parahippocampal gyrus and amygdala (Bogerts 1984), enlargement of the inferior horn of the lateral ventricle and reduced thickness of the parahippocampal gyrus (Brown et al. 1986). These results strongly support the hypothesis that dysfunction of limbic structures of the temporal lobe play a crucial role in the pathophysiology of schizophrenia (Stevens 1973, 1982; Torrey and Peterson 1974).

Furthermore, organic lesions (e.g. tumours, infarctions, traumata) of medial temporal lobe structures are frequently associated with clinical symptoms which are indistinguishable from "endogenous" schizophrenic symptoms suggesting common sites of pathology (Malamud 1967; Davison and Bagley 1969; Torrey and Peterson 1974).

Since pathological alterations within the brain are usually associated with loss of neurons and fibres and increased glial cell densities, we determined tissue volumes and numbers of pyramidal cells and glial cells in all parts of the hippocampal formation, which is the principal structure of the limbic system (Swanson 1983). To our knowledge, no such cell counts in the hippocampal formation of schizophrenics have previously been performed.

Offprint requests to: B. Bogerts at the above address

Material and Methods

Material

Complete coronal serial sections of brains from 13 schizophrenic patients (2 male, 11 female; age 43.4 ± 16.8 years [mean ± SD] Table 2) and 11 age-matched control cases (7 male, 4 female; 42.6 ± 19,6, Table 1) from the Vogt Institute of Brain Research, University of Düsseldorf, were investigated. The time between death and fixation of the brains was about the same in both groups (controls 2–36 h, schizophrenics 4–45 h. With the exception of 2 cases – 1 in each group – only left hemispheres were available for this study.

All brains were collected between 1928 and 1960, fixed by immersion in 4% formalin, embedded in paraffin, sectioned into 20 µm coronal serial sections and then Nissl-stained with the adjoining section being myelin-stained. All control cases had no neurological or psychiatric disease. None of the patients had received convulsive therapy, insulin therapy or neuroleptic drugs. The time between first diagnosis of the illness and death, ranged from 10 months to 24 years (mean 9.0 years). Of the schizophrenic patients, 5 had a predominant paranoid-hallucinatory symptomatology (ICD-9 295.3), 4 had predominant catatonic symptoms (ICD-9 295.2) and 4 had alternating periods of catatonic, paranoid and hebephrenic symptoms (undifferentiated type, mixed type). Further details of patients and controls are given in Tables 1 and 2.

Methods

Volume Determination. All parts of the hippocampal formation were outlined on projected enlargements (10 ×) of myelin-

stained coronal serial sections. The Nissl sections (15 ×) were used for volume determination of the granular cell layer. The distance between the sections was 0.5–1.0 mm, and they were evenly distributed from the rostral pole of the hippocampal formation up to the level of the posterior pole of the pulvinar. Details of volume determination by planimetry of serial sections have been described previously (Lesch and Bogerts 1984).

On myelin-stained sections the following subfields of the hippocampal formation could be clearly delineated (Fig. 1): alveus and fimbria hippocampi, perforant path, CA1 and CA2 (together), CA3, CA4, prosubiculum and subiculum (together), presubiculum and parasubiculum (together) and the volume of the whole hippocampal formation excluding the parahippocampal gyrus. CA1, and CA2, prosubiculum and subiculum and pre- and parasubiculum were evaluated together, as a reliable separation of these segments was not possible on the myelin-stained sections.

Outlining, planimetry and cell counts were done blind, i.e. without knowledge of the diagnosis by the individual performing the measurements. To allow for shrinkage of paraffin material during histological preparation and to obtain fresh volumes, the volumes calculated from serial sections were corrected by an average shrinkage factor of 1.89. This value has been determined previously in 30 brains from the Vogt collection (Lange et al. 1976).

Cell Densities. Cell densities were expressed as numbers of cells per tissue unit volume. In each brain 8 to 10 Nissl-stained sections were evaluated, 4 to 5 in the anterior and 4 to 5 in the posterior portion of the hippocampal formation (Fig. 1). The distance between the Nissl-stained sections chosen for cell counts was 1 mm.

In each section, densities of the pyramidal cells were determined by counting nuclei instead of cell bodies at a magnification of × 200, densities of glial cells by counting glial nuclei at a magnification of × 200. Different types of glial cells were not counted separately. Cell densities were evaluated in the following hippocampal segments: granular cell layer of the dentate fascia, CA1/CA2, CA3, CA4, subiculum/prosubiculum and presubiculum/parasubiculum. In each section of these areas four microscopic fields were evaluated. Further methodological details of cell counting have been described elsewhere (Bogerts 1977; Bogerts et al. 1983).

Absolute Cell Numbers. Absolute numbers of nerve cells and glial cells were calculated by multiplying numerical cell dens-

Table 1. Control cases without neurological or psychiatric disease. Brains were collected between the years 1928 and 1960

Brain	Age	Sex	Cause of death
A 56	56	M	Laryngeal cancer, death under operation
A 58	24	M	Haemorrhagic shock
A 61	38	M	Uraemic coma
A 64	84	M	Pneumonia
A 80	33	F	Carcinoma of the uterus
A 81	29	F	Unknown
A 85	30	F	Fat embolism after a street accident
A 88	62	M	Carcinoma of the stomach, peritonitis
A 97	39	M	Pulmonary embolism
A100	19	M	Aspiration pneumonia
A102	41	F	Cardiac arrest

Table 2. Schizophrenic cases. The brains were collected before the introduction of neuroleptic drugs, between the years 1930 and 1941

Brain	Age	Sex	Cause of death, year of death	Most prominent psychiatric symptoms	Time between diagnosis and death
Bu 3	22	F	Cardiac arrest, 1930	Persecution complex, acoustic hallucinations, mutism, negativism	3½ years
Bu 7	74	F	Myocardial infarction, 1930	Paranoid ideas, acoustic hallucinations, mutism, manierism	24 years
Bu 9	59	F	Bronchopneumonia, 1930	Paranoid ideas, optic hallucinations, coenaesthetic symptoms	4 years
Bu 12	51	F	Bronchopneumonia, 1930	Persecution complex, stupor, negativism, mutism	Not known
Bu 19	44	F	Pneumonia, 1930	Paranoid ideas, feeling of being watched, acoustic hallucinations	11 months
Bu 20	26	F	Bronchopneumonia, 1930	Stupor, catatonia, mutism	7 years
Bu 21	42	F	Pneumonia, 1930	Stupor, mutism, flexibilitas cerea, acoustic hallucinations	6½ years
Bu 24	27	F	Bronchopneumonia, 1930	Optic, acoustic and haptic hallucinations, stereotype movements, manierism, hebephrenic symptoms	4 years
Bu 46	19	F	Cardiac illness, 1932	Rigid postures, drawing faces, negativism	Not known
Bu 52	24	M	Bronchopneumonia, 1933	Stupor, stereotypy in posture and movement, catatonia, catalepsy	3 years
Bu 62	64	F	Suicide, 1933	Delusions, hallucinations, persecution complex	23 years
Bu 89	43	F	Pneumonia, 1935	Acoustic hallucinations, paranoid ideas, feeling of electrical stimulation	13 months
Cp 81	39	M	Not known, 1941	Hebephrenic symptoms, drawing faces, delusions, manierism, mutism	22 years

ities × tissue volume. This value is independent of tissue shrinkage.

Criteria of Delineation

Myelin-stained Sections for Volume Determinations. The hippocampal formation was defined according to the criteria of Chronister and White (Chronister and White 1975), including the hippocampus proper, prosubiculum, subiculum, pre- and parasubiculum (Fig. 1). The entorhinal region and the whole parahippocampal gyrus (both regions overlap in part) were excluded in this study.

The following criteria were used to separate hippocampal subfields: CA4 situated within the dentate fascia terminated at the hilus of the dentate fascia (Lorente de No 1934), the mossy fibre system of CA4/CA3 abruptly terminated at the border to CA2 (Braak 1974). No sharp delineation between CA1 and CA2 was possible, therefore these two segments were evaluated together.

Myelin bundles crossing the pyramidal cell layer vertically were typical for prosubiculum and subiculum (Rose 1938; Lorente de No 1934); pre- and parasubiculum were characterized by a relative dense plexus of fine myelin fibres (Lorente de No 1934). To separate pre- and parasubiculum from the parahippocampal gyrus an artificial line was drawn using the medial corner of the fissura hippocampi as a topographical marker point as shown in Fig. 1; more precise separation was not possible in myelin sections.

The granular cell layer of the dentate fascia could not clearly be delineated in myelin-stained sections; therefore, volume determination and cell counts were performed on the Nissl-stained sections.

Nissl-Stained Sections for Cell Counts. In coronal sections, the structure of the anterior parts of the hippocampal formation differed from that of the posterior parts. CA1, CA2, CA3, and CA4 were delineated according to Rose (Rose 1938), and Lorente de No (Lorente de No 1934); the subicular subfields were delineated as described by Braak (1972).

Statistics

Because of the inhomogenous sex distribution, two-way analysis of variance and covariance (diagnosis by sex) with repeated measures on the second factor were performed, using programme package and statistical software of BMDP 7D. Description of groups with histograms and analysis of variance were performed on a Siemens BS 2000 Computer (University of Düsseldorf).

P-values of normals (n) versus schizophrenics (s) and males (M) versus females (F) are given in the following results. Mean differences are given in Tables 3–5.

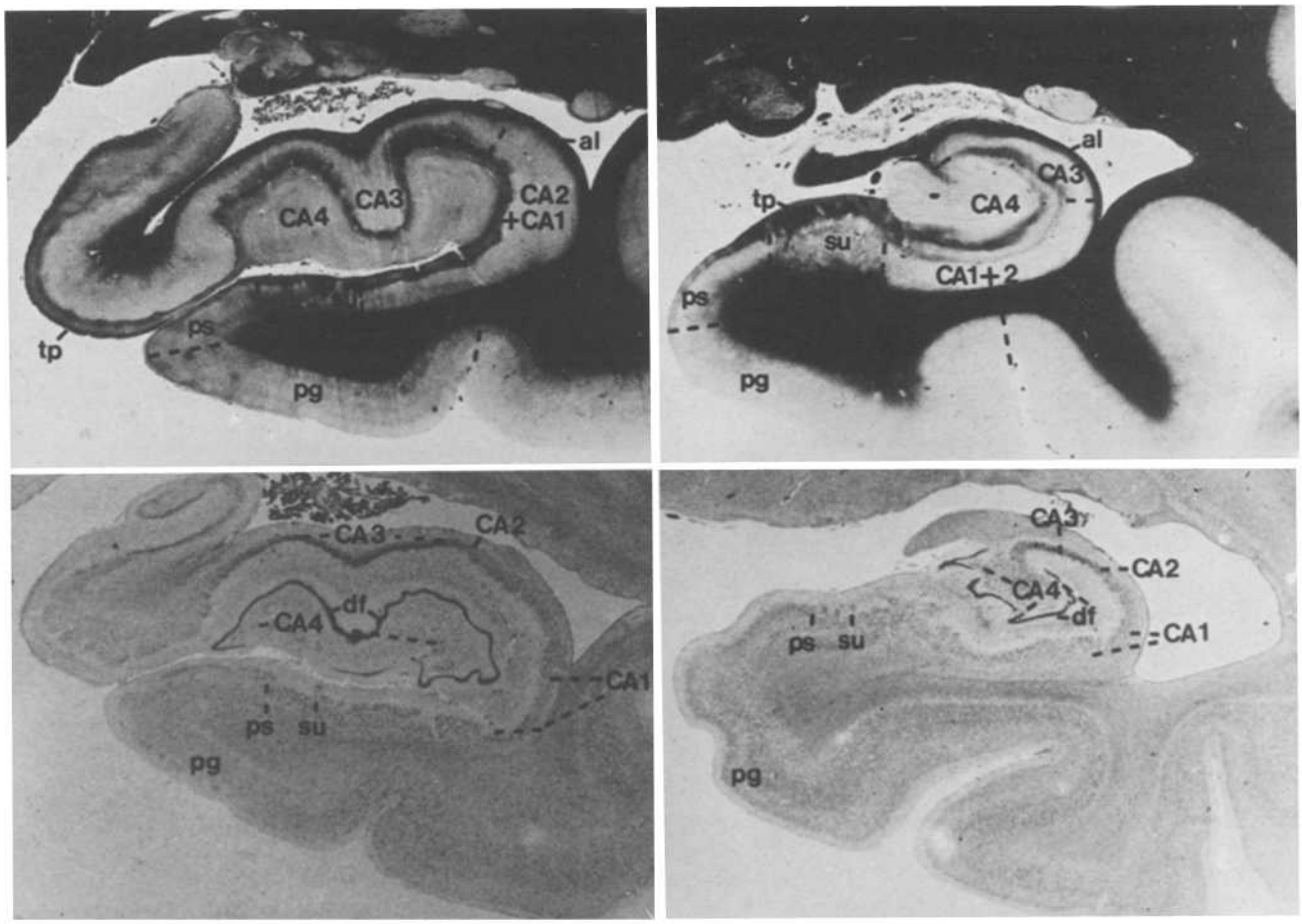

Fig. 1. Two myelin- *(top)* and two Nissl-stained *(bottom)* coronal sections of the anterior part *(left)* and the posterior part *(right)* of the hippocampal formation (magnification 6 ×) showing the different anatomy of the CA segments and of the dentate gyrus at the two levels. Distance between the sections is about 2 cm. Criteria of delineation are given in the text. *al* = alveus, *tp* = tractus perforans, *df* = dentate fascia, *CA1–CA4* = hippocampus proper, *su* = prosubiculum/subiculum, *ps* = presubiculum/ parasubiculum, *pg* = parahippocampal gyrus

Table 3. Tissue volumes of the hippocampal formation and all hippocampal segments (values in mm^3)

Evaluated areas	Controls		Schizophrenics		Mean differences (controls = 100%)		*P* values	
	Males ($n = 7$) Mean (SD)	Females ($n = 4$) Mean (SD)	Males ($n = 2$) Mean (SD)	Females ($n = 11$) Mean (SD)	M (%)	F (%)	M vs F	c vs s
Total hippocampal formation	3493 (427)	3354 (403)	2708 (886)	2942 (384)	−22	−12	$P = 0.83$	$P = 0.01$
CA1/CA2	431 (67)	574 (83)	393 (59)	404 (95)	− 9	−30	$P = 0.08$	$P = 0.02$
CA3	826 (145)	706 (132)	535 (116)	680 (158)	−35	+ 4	$P = 0.87$	$P = 0.04$
CA4	445 (52)	459 (101)	339 (124)	343 (69)	−24	−25	$P = 0.81$	$P = 0.007$
Total pyramidal band of the hippocampal formation	2200 (244)	2190 (239)	1638 (376)	1861 (275)	−26	−14	$P = 0.43$	$P = 0.003$
Prosubiculum/subiculum	227 (53)	197 (36)	236 (74)	194 (45)	+ 4	− 2	$P = 0.15$	$P = 0.91$
Presubiculum/parasubiculum	280 (77)	270 (68)	180 (66)	237 (56)	−29	−12	$P = 0.48$	$P = 0.05$
Granular cell layer of dentate fascia	876 (189)	1026 (233)	774 (439)	709 (176)	−12	−31	$P = 0.68$	$P = 0.05$
Alveus and fimbria hippocampi	517 (115)	444 (81)	393 (150)	428 (64)	−24	− 4	$P = 0.68$	$P = 0.13$
Perforant path	775 (96)	682 (137)	603 (249)	654 (97)	−22	− 4	$P = 0.71$	$P = 0.10$

Mean, standard deviation (SD), number of sample (n), mean differences given separately for male (M) and female (F) cases. *P* values of controls (c) vs schizophrenics (s) and males (M) vs females (F)

Table 4a. Absolute numbers of pyramidal cells ($\times 10^6$). For abbreviations see Table 3

Evaluated areas	Controls		Schizophrenics		Mean differences (controls = 100%)		*P* values	
	Males ($n = 7$) Mean (SD)	Females ($n = 4$) Mean (SD)	Males ($n = 2$) Mean (SD)	Females ($n = 11$) Mean (SD)	M (%)	F (%)	M vs F	c vs s
CA1/CA2	27 (4)	32 (9)	25 (1)	21 (6)	− 6	−36	$P = 0.88$	$P = 0.04$
CA3	54 (11)	37 (11)	39 (3)	34 (7)	−28	− 7	$P = 0.03$	$P = 0.05$
CA4	21 (3)	13 (3)	15 (3)	12 (4)	−28	− 4	$P = 0.003$	$P = 0.05$
Prosubiculum/subiculum	10 (2)	7 (1)	11 (2)	8 (2)	+14	+15	$P = 0.004$	$P = 0.20$
Presubiculum/parasubiculum	8 (3)	8 (2)	7 (0.5)	7 (2)	−19	−19	$P = 0.85$	$P = 0.17$
Granular cell layer of the dentate fascia	18 (6)	23 (8)	14 (11)	15 (4)	−20	−32	$P = 0.31$	$P = 0.07$

Table 4b. Absolute numbers of glial cells ($\times 10^6$). For abbreviations see Table 3

Evaluated areas	Controls		Schizophrenics		Mean differences (controls = 100%)		*P* values	
	Males ($n = 7$) Mean (SD)	Females ($n = 4$) Mean (SD)	Males ($n = 2$) Mean (SD)	Females ($n = 11$) Mean (SD)	M (%)	F (%)	M vs F	c vs s
CA1/CA2	96 (16)	102 (29)	80 (4)	90 (20)	−17	−11	$P = 0.41$	$P = 0.17$
CA3	270 (60)	169 (21)	139 (25)	204 (31)	−48	+21	$P = 0.38$	$P = 0.03$
CA4	142 (24)	128 (35)	101 (41)	110 (26)	−28	−13	$P = 0.83$	$P = 0.05$
Prosubiculum/subiculum	94 (20)	66 (5)	71 (6)	80 (19)	−24	+23	$P = 0.30$	$P = 0.63$
Presubiculum/parasubiculum	148 (38)	113 (21)	73 (18)	122 (21)	−51	+ 9	$P = 0.62$	$P = 0.03$

Results

Volumes

The volume of the whole hippocampal formation was reduced in the schizophrenic group (n vs s: $P = 0.01$), there was no significant sex difference in hippocampal volume (Table 3). The volumes of the following hippocampal substructures were significantly reduced in schizophrenics: CA1/CA2 (n vs s: $P = 0.02$), CA3 (n vs s: $P = 0.04$), CA4 (n vs s: $P = 0.007$), pre- and parasubiculum (n vs s: $P = 0.05$), granular cell layer of the dentate fascia (n vs s: $P = 0.05$). The whole band of pyramidal cells (CA1–CA4) was highly significantly reduced (n vs s: $P = 0.003$). No volume difference of the subiculum/prosubiculum, alveus and fimbria hippocampi was found. The perforant path showed a trend towards volume reduction (n vs s: $P = 0.10$).

Pyramidal Cells

Schizophrenics exhibited a significant loss of neurons in CA1/CA2 (n vs s: $P = 0.04$), CA3 (n vs s: $P = 0.05$) and CA4 (n vs s: $P = 0.05$) (Table 4a). There was a trend towards reduction of granular cells of the dentate fascia (n vs s: $P = 0.07$). The

Table 5. Densities of pyramidal cells (× 100/mm³). For abbreviations see Table 3

Evaluated areas	Controls				Schizophrenics				Mean differences (controls = 100%)		P values	
	Males ($n = 7$) Mean	(SD)	Females ($n = 4$) Mean	(SD)	Males ($n = 2$) Mean	(SD)	Females ($n = 11$) Mean	(SD)	M (%)	F (%)	M vs F	c vs s
CA1/CA2	63	(7)	49	(6)	59	(11)	51	(11)	− 6	+ 4	$P = 0.03$	$P = 0.79$
CA3	66	(7)	50	(5)	75	(20)	52	(11)	+14	+ 4	$P = 0.001$	$P = 0.27$
CA4	47	(7)	31	(6)	50	(6)	39	(9)	+ 7	+24	$P = 0.002$	$P = 0.19$
Prosubiculum/subiculum	44	(5)	34	(4)	45	(7)	41	(8)	+ 2	+22	$P = 0.05$	$P = 0.23$
Presubiculum/parasubiculum	31	(8)	31	(2)	35	(11)	32	(5)	+13	+ 3	$P = 0.53$	$P = 0.43$
Granular cell layer of the dentate fascia	204	(39)	198	(19)	210	(60)	222	(44)	+ 3	+12	$P = 0.87$	$P = 0.49$

cell numbers were unchanged in the prosubiculum/subiculum and the pre-/parasubiculum.

In contrast to the volume values which revealed no sex differences, the absolute cell numbers of CA3, CA4, prosubiculum/subiculum were smaller in females than in males. As shown below, the smaller absolute cell numbers in females were due to significant sex dependent differences in cell densities, volumes being unchanged.

Glial Cells

Since loss of neurons in brain diseases is usually associated with gliosis, densities and absolute numbers of glial cells were determined without separation into subtypes (i.e. astrocytes, oligodendrocytes, Hortega cells).

Surprisingly, the results showed opposite trends for males and females. Schizophrenic males tended to have reduced absolute numbers of glial cells in CA1/CA2 (−17%), CA3 (−48%), CA4 (−28%), prosubiculum/subiculum (−24%), pre-/parasubiculum (−51%), schizophrenic females exhibiting increased numbers of glial cells in CA3 (+21%), prosubiculum/subiculum (+23%), pre-/parasubiculum (+9%), in comparison to the controls (Table 4b).

Differences in glial cell numbers were significant for normals versus schizophrenics in CA3 ($P = 0.03$), CA4 ($P = 0.05$) and pre-/parasubiculum ($P = 0.03$).

Densities of Pyramidal Cells

Although there was a loss of pyramidal cells in most segments of the hippocampal formation of schizophrenics, no differences in pyramidal cell densities were revealed in any of the evaluated areas. Since drop out of nerve cells can cause tissue shrinkage that in turn may lead to an artificial increase in cell densities, absolute cell numbers, which are independent of tissue shrinkage, might be more reliable to assess neuronal loss than cell densities (Table 5).

Significant sex differences were detected in CA 1/CA2 (n vs s: $P = 0.79$), CA3 (n vs s: $P = 0.27$), CA4 (n vs s: $P = 0.19$) and prosubiculum/subiculum (n vs s: $P = 0.23$) (Table 5).

Differences Between Diagnostic Subgroups

The most distinct loss of hippocampal pyramidal cells occurred in the paranoid-hallucinatory subgroup. In these patients there was a loss of pyramidal cells in CA1/CA2 (n vs s: $P = 0.015$, Fig. 2), CA3 (n vs s: $P = 0.005$, Fig. 3) and CA4 (n vs s: $P = 0.003$, Fig. 4). The catatonics exhibited a less distinct but also significant loss of pyramidal cells in CA4 (n vs s: $P = 0.03$, Fig. 4) and dentate fascia (n vs s: $P = 0.03$, Fig. 6); in the mixed-type subgroup there was a significant reduction of pyramidal cells in CA3 (n vs s: $P = 0.05$, Fig. 3) and CA4 (n vs s: $P = 0.05$, Fig. 4).

Beside the diagnostic classification the following subgroups were compared:

- patients with hereditary factors versus patients without hereditary factors,
- patients with long duration of illness versus patients with short duration of illness (more or less than 4 years),
- early-onset patients versus young controls (younger than 40 years),
- late-onset patients versus old controls (older than 40 years),
- early-onset cases versus late-onset cases (earlier/later than 40 years)

No significant difference could be found in any of these subgroups.

Discussion

The present data reveal that volume reduction of the hippocampal formation of schizophrenics is associated with reduced numbers of pyramidal cells in the segments CA1/CA2, CA3, CA4, whereas cell numbers of the prosubiculum/subiculum and pre-/parasubiculum are unchanged. There is a trend towards loss of granular cells in the dentate fascia. The reduction of hippocampal pyramidal cells was more distinct in the paranoid-hallucinatory subgroup than in catatonic or undifferentiated schizophrenics.

The major problem in morphometric evaluation of post mortem brain tissue is to ensure that differences between patients and controls reflect actual pathological changes and are not the result of factors unrelated to the disease such as autolysis, duration and kind of the terminal disease and the histological processing itself. Three of the controls but only one schizophrenic patient had long lasting terminal diseases (e.g. cancer, Tables 1 and 2), the other controls and schizophrenics had acute causes of death (myocardial infarction, bronchopneumonia, pulmonary embolism). During the long period of collection of the brains (1928–1960), the Vogt's and their coworkers took great care to ensure constant histological processing (fixation, embedding and cutting). The mean death to

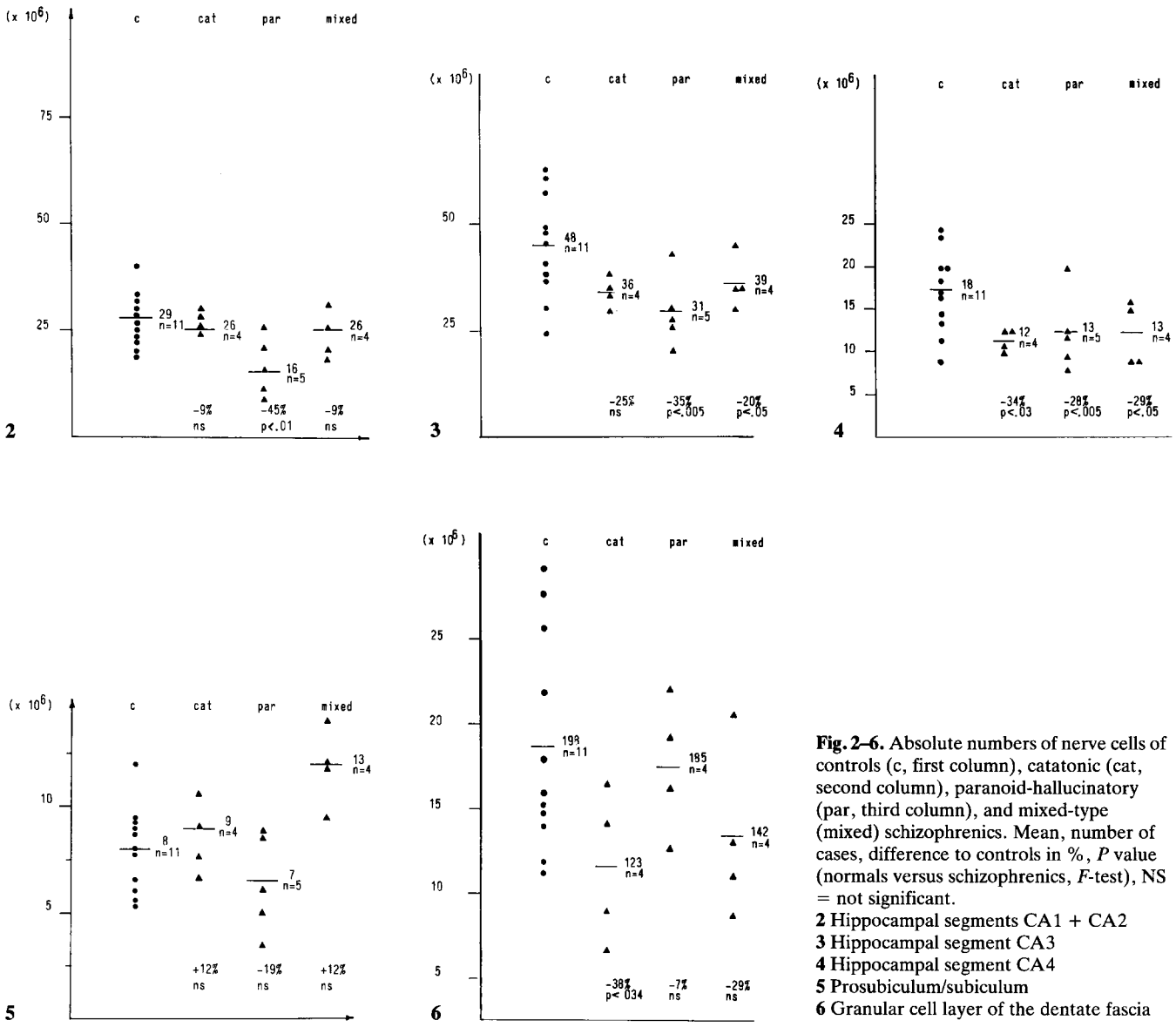

Fig. 2–6. Absolute numbers of nerve cells of controls (c, first column), catatonic (cat, second column), paranoid-hallucinatory (par, third column), and mixed-type (mixed) schizophrenics. Mean, number of cases, difference to controls in %, *P* value (normals versus schizophrenics, *F*-test), NS = not significant.
2 Hippocampal segments CA1 + CA2
3 Hippocampal segment CA3
4 Hippocampal segment CA4
5 Prosubiculum/subiculum
6 Granular cell layer of the dentate fascia

post mortem delay was almost identical in both groups. Thus, it is unlikely that the differences were secondary to a non-cerebral medical illness or to histological or autolytic artefacts.

Further problems of this study were that the groups were not sex matched, that numbers of male schizophrenics and female controls were small, and that nerve cell densities and absolute numbers of neurons differed between males and females. Two way analysis of variance and covariance revealed, however, not only significant sex differences but also significant differences between patients and controls. We only investigated brains of patients never treated with neuroleptics, insulin, or electric shock; therefore artefacts due to modern medical treatment can be excluded. Nevertheless, we are aware that the results presented are preliminary and need corroboration by studies of larger and sex matched samples. In the Vogt collection no more schizophrenic and control cases were available.

The values of the mean densities of nerve cells in hippocampal CA segments of the controls corresponded roughly to those found in the human brains by other authors (Ball 1977; Mouritzen Dam 1979; Devaney and Johnson 1984).

Our finding of sexual dimorphism in nerve cell densities is not entirely surprising, since marked sex dependent differences in biochemical and neurophysiological data of the hippocampus have been published previously (Foy et al. 1984; Swaab and Hofmann 1984; Juraska 1984).

Only one other study has quantitatively examined the histology of the hippocampal formation of schizophrenics (Scheibel and Kovelman 1984). The authors did not determine volumes of hippocampal subfields or absolute cell numbers, but found a significant disarray of the pyramidal cells which was interpreted as a morphological correlate of disturbed function of the hippocampus.

Our data also indicate that the function of the hippocampus is insufficient in schizophrenia, for it is known from all degenerative brain diseases, that reduction of brain tissue and drop out of nerve cells causes impaired functioning of the affected brain parts.

The mean number of glial cells in the schizophrenic group as a whole was not significantly different from controls; therefore reduction of hippocampal nerve cells in schizophrenia is not generally accompanied by gliosis. There were however op-

posite trends for males and females within the schizophrenic group, males exhibiting a decrease, females an increase in glial cell numbers. With respect to the small number of male schizophrenics no definite explanation can be given for this finding, but it is conceivable that at least in a subgroup of schizophrenics, nerve cells and glial cells are affected by the disease.

The present knowledge of the neurophysiology of the hippocampal formation allows an attempt at explaining why dysfunction of this structure causes at least some symptoms commonly seen in schizophrenia. Schizophrenics seem to suffer from a lack of "sensory gating" (Asarnow and MacCrimmon 1982; Franks et al. 1983; Baribeau-Braun et al. 1983; Schwartz et al. 1983; Siegel et al. 1984), meaning that schizophrenics are unable to filter out irrelevant sensory input and fail to discriminate relevant from irrelevant stimuli. The hippocampus seems to play a crucial role in this "sensory gating", for it receives and integrates information from all sensory modalities (Papez 1937; Roberts 1963; Pandya and Seltzer 1982; Swanson 1983). If the information is not familiar, the hippocampus loses its inhibitory effect on hypothalamic and brainstem structures involved in attention; the subject reacts to the new stimulus. If the stimulus is familiar, it is filtered out and the subject continues with its ongoing behaviour (Pribram and McGuiness 1975; Schmajuk 1984). Thus, damaged structure of the hippocampus seems to contribute to the complex picture of schizophrenia. Our finding that the highest loss of neurons occurs in paranoid-hallucinatory patients agrees well with reports (Halgren et al. 1983) that sensory gating is most disturbed in paranoid schizophrenics.

Structural damage of the hippocampus is not specific for schizophrenia, it also occurs in temporal lobe epilepsy (Scheibel et al. 1974; Mouritzen Dam 1980; Babb et al. 1984) in which CA4 is most damaged, in Alzheimer's disease (Probst et al. 1983; Hyman et al. 1984; Ball et al. 1985) and Pick's disease (Jellinger and Grisold 1980). While temporal lobe epileptics sometimes display schizophrenia-like symptoms, Alzheimer and Pick patients usually do not.

Therefore we assume that structural damage to the hippocampus only under the influence of additional, as yet undefined factors, which are not present in other brain diseases with hippocampal damage (e.g. Alzheimers disease), predisposes to the development of schizophrenic symptoms.

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