HIPPOCAMPAL PATHOLOGY IN SCHIZOPHRENIA A MORPHOMETRIC STUDY

DISSERTATION
zur Erlangung des Grades eines Doktors der Medizin
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vorgelegt von
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I. INTRODUCTION

Recently, several well controlled morphometric studies of post mortem brains could demonstrate independently pathological alterations in limbic structures of the medial temporal lobe of schizophrenics.

The main findings were altered orientation of hippocampal pyramidal cells (Kovelman and Scheibel, 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 plays a crucial role in the pathophysiology of schizophrenia (Stevens, 1973, 1982; Torrey and Peterson, 1974).

Furthermore, organic lesions (e.g. tumors, 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, tissue volumes and numbers of pyramidal cells and glial cells were determined in all parts of the hippocampal formation, which is the principal structure of the limbic system (Swanson, 1983).
To my knowledge, no such cell counts in the hippocampal formation of schizophrenics have previously been performed.
II. MATERIAL

Complete coronal serial sections of brains from 13 schizophrenic patients (2 male, 11 female; age $43.3 \pm 16.8$ years (mean \pm SD) Table 2) and 11 age-matched control cases (7 male, 4 female; $42.6 \pm 19.6$, Table 1) of the C. and O. 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 two cases - one 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, cut in 20 µm coronal serial sections and then Nissl-stained and - the adjoining section - myelin-stained. All control cases had no neurological or psychiatric diseases. None of the patients had convulsive, insulin or neuroleptic therapy. The time between first diagnosis of the illness and death, ranged from 10 months to 24 years (mean 9.0 years). 5 of the schizophrenic patients had a predominant paranoid-hallucinatory symptomatology (ICD-9 295.3), 4 schizophrenics 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 Table 1 and 2.
III. METHODS

1. **Volume determination**

All parts of the hippocampal formation were outlined on projected enlargements (10x) of myelin-stained coronal serial sections. Only for volume determination of the granular cell layer Nissl-sections (15x) were used. The distance between the sections was 0.5-1.0 mm, 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 (see Figure 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 blindly, i.e. without knowledge of the diagnosis by the individual performing the measurements.

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 of the Vogt
collection (Lange et al., 1976).

2. **Cell densities**

Cell densities are expressed as numbers of cells per tissue unit volume.

8 to 10 Nissl stained sections were evaluated in each brain, 4-5 in the anterior and 4-5 in the posterior portion of the hippocampal formation (Figure 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 x200, densities of glial cells by counting glial nuclei at a magnification of x200. 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 are given elsewhere (Bogerts, 1977; Bogerts et al., 1983).

3. **Absolute cell numbers**

Absolute numbers of nerve cells and glial cells were calculated by multiplying numerical cell densities x tissue volume. This value is independent of tissue shrinkage.
IV. CRITERIA OF DELINEATION

1. Myelin stained sections for volume determinations (Figure 1)

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 (Figure 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 terminates at the hilus of the dentate fascia (Lorente de No, 1934), the mossy fibre system of CA4/CA3 abruptly terminates at the border to CA2 (Braak, 1974). No sharp delineation between CA1 and CA2 was possible, therefore these two segments were evaluated together.

Typical for the prosubiculum and subiculum are myelin bundles crossing the pyramidal cell layer vertically (Rose, 1938; Lorente de No, 1934); the pre- and parasubiculum are 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 Figure 1; a more precise separation was not possible on myelin sections.

The granular cell layer of the dentate fascia could not clearly be delineated on myelin stained sections; therefore, volume determination and cell counts were performed on the Nissl stained sections.
2. *Nissl stained sections for cell counts* (Figure 1)

In coronal sections, the structure of the anterior parts of the hippocampal formation differs from that of the posterior parts. CA1, CA2, CA3, and CA4 were delineated according to Rose (Rose, 1934), and Lorente de Nó (Lorente de Nó, 1934); the subicular subfields were delineated as described by Braak (Braak, 1972).
V. 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 soft ware 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 (vs) schizophrenics (s) and males (m) vs females (f) are given in the following results.

Mean differences are given in the Tables 3 - 5.
VI. RESULTS

1. **Volumes** (Table 3)

The volume of the whole hippocampal formation was reduced in the schizophrenic group (n vs s: p = .01), there was no significant sex difference in hippocampal volume.

The volumes of the following hippocampal substructures were significantly reduced in schizophrenics: CA1/CA2 (n vs s: p = .02), CA3 (n vs s: p = .04), CA4 (n vs s: p = .007), pre- and parasubiculum (n vs s: p = .05), granular cell layer of the dentate fascia (n vs s: p = .05).

The whole band of pyramidal cells (CA1 - CA4) was highly significantly reduced (n vs s: p = .003). No volume difference of the subiculum/parasubiculum, alveus and fimbria hippocampi could be found.

The perforant path showed a trend towards volume reduction (n vs s: p = .10).

2. **Absolute numbers of pyramidal cells and glial cells**

(Table 4a and 4b)

Schizophrenics exhibit a significant loss of neurons in CA1/CA2 (n vs s: p = .04), CA3 (n vs s: p = .05) and CA4 (n vs s: p = .05).

There was a trend towards a reduction of granular cells of the dentate fascia (n vs s: p = .07).

The 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 lower in females than in males. As shown below, the lower absolute cell numbers in females are due to significant sex dependent differences in cell densities, volumes being unchanged.

3. Glial cells (Table 4b)

Since loss of neurons in brain diseases is usually associated with gliosis, densities and absolute numbers of glial cells were determined without separation in 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.

Differences in glial cell numbers were significant for normals versus schizophrenics in CA3 (p = .03), CA4 (p = .05) and pre-/parasubiculum (p = .03).
4. Densities of pyramidal cells (Table 5)

Although there was a loss of pyramidal cells in most segments of the hippocampal formation of schizophrenics, no differences in pyramidal cell densities could be 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 then cell densities.

Significant sex differences could be detected in CA1/CA2 (n vs s: p = .79), CA3 (n vs s: p = .27), CA4 (n vs s: p = .19) and prosubiculum/subiculum (n vs s: p = .23).

5. Differences between diagnostic subgroups (Figure 2 - 6)

The most distinct loss of hippocampal pyramidal cells occurs in the paranoid-hallucinatory subgroup, in these patients there is a loss of pyramidal cells in CA1/CA2 (n vs s: p = .015, Figure 2), CA3 (n vs s: p = .005, Figure 3), CA4 (n vs s: p = .003, Figure 4), prosubiculum/subiculum (n vs s: p = .001, Figure 5).

The catatonics exhibited a less distinct but also significant loss of pyramidal cells in CA4 (n vs s: p = .03, Figure 4) and dentate fascia (n vs s: p = .03, Figure 6); in the mixed-type subgroup there was a significant reduction of pyramidal cells in CA3 (n vs s: p = .05, Figure 3), CA4 (n vs s: p = .05, Figure 4) and prosubiculum/subiculum (n vs s: p = .02, Figure 5).

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.
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 granule 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. 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 collecting the brains (1928 - 1960), the Vogt's and their coworkers took great care of a constant histological processing (fixation, embedding and cutting). The mean interval between death and autopsy was nearly identical in both groups. Thus, it is unlikely that the differences were secondary to a non-cerebral medical illness or due 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 cell 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 electrical shocks; 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 schizophrenics and control cases were available.

The values of the mean densities of nerve cells in hippocampal CA-segments of the controls correspond roughly to those found in the human brains by other authors (Ball, 1977; Mouritzen Dam, 1978; 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; Juraske, 1984).

There exists only one other study which examined quantitatively the histology of the hippocampal formation of schizophrenics (Scheibel and Kovelman, 1984). The authors neither determined volumes of hippocampal subfields nor 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, too, indicate that the function of the hippocampus is
altered 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 with gliosis. There were, however, opposite 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 to explain 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 Mac Crimmon, 1982; Franks et al., 1983; Baribeau-Braun et al., 1983; Schwartz et al., 1983; Siegel et al., 1984), by account of which schizophrenics are unable to filter out non-relevant sensory input and fail to discriminate relevant from non-relevant stimuli. The hippocampus seems to play a crucial role in this "sensory gating", for it receives and integrates informations from all sensory modalities (Papez, 1937; Roberts, 1963; Pandya, 1982; Swanson, 1983). If the information is not familiar, the hippocampus breaks of its inhibitory effect on hypothalamic and brainstem structures involved in attention; the subjects reacts to
the new stimulus. If the stimulus is familiar, it is filtered out; the subject continues with its ongoing behaviour (Pribram and McGiuness, 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 fits well to reports (Halgreen 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., 1984; Mouritzen Dam, 1980; Babb et al., 1984) in which CA4 is damaged most, in Alzheimer’s disease (Probst et al., 1983; Hyman et al., 1984; Ball, 1985) and Pick’s disease (Jellinger and Grisold, 1982). While temporal lobe epileptics sometimes display schizophrenia-like symptoms, Alzheimer and Pick patients do usually not, since only older patients suffer from Alzheimer’s disease and Pick’s disease and since the schizophrenic symptoms begin usually in adolescence and decline during old age, assume that structural damage of the hippocampus, only under the influence of age related factors (which are not present in senile dementias) predisposes to the development of schizophrenic symptoms.

In this connection it is of interest that the gonadal steroids testosterone and estrogen have a strong influence on the neuronal activity of hippocampal pyramidal cells (Mc Gowan-Sass, Timiras 1975). Therefore it can be hypothesized that a damaged hippocampus decompensates definitively under the influence of gonadal steroids, thus giving rise to the development of schizophrenic symptoms.
Acknowledgments: The author wishes to thank Dr. B. Bogerts for his personal advice as well as many valuable discussions and Mrs. B. Machus for excellent technical assistance.
VIII. REFERENCES

Asarnow RF, MacCrimmon DJ (1982) Attention/information processing, neuropsychological functioning, and thought disorder during the acute and partial recovery phases of schizophrenia: a longitudinal study. Psychiatry Res 7: 309-319


Brown et al. (1986) Volume increase of the inferior horn of the lateral ventricle in schizophrenic patients. Arch Gen Psychiatry 43: 36-42


Lorente de No R (1934) Studies on the structure of the cerebral cortex. II. Continuation of the study of the ammonic system. J Psychol Neurol 46 (2, 3): 113-177

Malamud N (1967) Psychiatric disorder with intracranial tumors of the limbic system. Arch Neurol 17: 113-123


Trends Neurosci 5: 386-390

38: 725-743

The Hippocampus. Vol 2: Neurophysiology and behavior. Plenum Press,
New York and London, pp 429-441

dementia of Alzheimer type: a Golgi analysis in the hippocampal
region. Brain Res 268: 249-254


Rose J (1938) Zur normalen und pathologischen Architektur der Ammons-
formation. J Psychol Neurol 49 (1, 2): 137-186

Scheibel AB, Kovelman JA (1984) A neurohistological correlate of schizo-
phrenia. Biol Psychiatry 19 (12): 1601-1621

Scheibel ME, Crandall PH, Scheibel AB (1974) Complex in temporal lobe
epilepsy. Epilepsia 15: 55-80

Physiol Psychol 12 (3): 166-183

visual information processing by chronic schizophrenics. Biol Psychiatry 18 (11): 1311-1320

sensory gating in schizophrenic patients and their relatives. Arch Gen Psychiatry 41: 607-612

Stevens JR (1973) An anatomy of schizophrenia? Arch Gen Psychiatry 29:
177-189

Stevens JR (1982) Neuropathology of schizophrenia. Arch Gen Psychiatry
39: 1131-1139


Swanson LW (1983) The hippocampus and the concept of the limbic system.

Lancet 2: 942-946
IX. TABLES

<table>
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<tr>
<th>Brain</th>
<th>Age</th>
<th>Sex</th>
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<tbody>
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<td>A 56</td>
<td>56</td>
<td>m</td>
<td>Laryngeal cancer, death under operation</td>
</tr>
<tr>
<td>A 58</td>
<td>24</td>
<td>m</td>
<td>Haemorrhagic shock</td>
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<td>A 61</td>
<td>38</td>
<td>m</td>
<td>Uraemic coma</td>
</tr>
<tr>
<td>A 64</td>
<td>84</td>
<td>m</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>A 80</td>
<td>33</td>
<td>f</td>
<td>Carcinoma of the uterus</td>
</tr>
<tr>
<td>A 81</td>
<td>29</td>
<td>f</td>
<td>unknown</td>
</tr>
<tr>
<td>A 85</td>
<td>30</td>
<td>f</td>
<td>Fat embolism after a street accident</td>
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<tr>
<td>A 88</td>
<td>62</td>
<td>m</td>
<td>Carcinoma of the stomach, peritonitis</td>
</tr>
<tr>
<td>A 97</td>
<td>39</td>
<td>m</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>A 100</td>
<td>19</td>
<td>m</td>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td>A 102</td>
<td>41</td>
<td>f</td>
<td>Cardiac arrest</td>
</tr>
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</table>

*Table 1*: Control cases without neurological or psychiatric disease. Brains were collected between the years 1928 and 1960.
Table 2: Schizophrenic cases. The brains were collected before the introduction of neuroleptic drugs, between the years 1930 and 1941.
<table>
<thead>
<tr>
<th>Evaluated areas</th>
<th>Controls</th>
<th>Schizophrenics</th>
<th>Mean diff. (Controls = 100 %)</th>
<th>p-values</th>
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<tbody>
<tr>
<td></td>
<td>Males (n=7)</td>
<td>Females (n=4)</td>
<td>Males (n=2)</td>
<td>Females (n=11)</td>
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<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td></td>
<td>(m) f</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
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<tr>
<td>total hippocampal formation</td>
<td>3493 (427)</td>
<td>3354 (403)</td>
<td>2700 (886)</td>
<td>2942 (384)</td>
</tr>
<tr>
<td></td>
<td>-22</td>
<td>-12</td>
<td>p = .83</td>
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<tr>
<td>CA1/CA2</td>
<td>431 (67)</td>
<td>574 (83)</td>
<td>393 (59)</td>
<td>404 (95)</td>
</tr>
<tr>
<td></td>
<td>-9</td>
<td>-30</td>
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<td>CA3</td>
<td>826 (145)</td>
<td>706 (132)</td>
<td>535 (116)</td>
<td>680 (158)</td>
</tr>
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<td></td>
<td>-35</td>
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<td>CA4</td>
<td>445 (52)</td>
<td>459 (101)</td>
<td>339 (124)</td>
<td>343 (69)</td>
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<td></td>
<td>-24</td>
<td>-25</td>
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<td>total pyramidal band of the hippocampal formation</td>
<td>2200 (244)</td>
<td>2190 (239)</td>
<td>1638 (376)</td>
<td>1861 (275)</td>
</tr>
<tr>
<td></td>
<td>-26</td>
<td>-14</td>
<td>p = .43</td>
<td>p = .003</td>
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<td>prosubiculum/</td>
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<td>197 (36)</td>
<td>236 (74)</td>
<td>194 (45)</td>
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<td>subiculum</td>
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<td>180 (66)</td>
<td>237 (56)</td>
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<td>1026 (233)</td>
<td>774 (439)</td>
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<td>p = .05</td>
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<td>parasubiculum</td>
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<td>444 (81)</td>
<td>393 (150)</td>
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<td>-4</td>
<td>p = .68</td>
<td>p = .13</td>
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<td>granular cell layer of dentate fascia</td>
<td>775 (96)</td>
<td>682 (137)</td>
<td>603 (249)</td>
<td>654 (97)</td>
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<tr>
<td></td>
<td>-22</td>
<td>-4</td>
<td>p = .71</td>
<td>p = .10</td>
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**Table 3:** Tissue volumes of the hippocampal formation and all hippocampal segments (values in mm³).

Mean, standard deviation (SD), number of sample (n), mean differences given separately for male (m) and female (f) cases. p-values of controls (c) versus (vs) schizophrenics (s) and males (m) versus females (f).
Evaluated areas | Controls | Schizophrenics | mean diff. | p-values
--- | --- | --- | --- | ---
Males (n=7) | Females (n=4) | Males (n=2) | Females (n=11) | (Controls = 100 %) | m vs f | c vs s

| Mean | Mean | Mean | Mean | (SD) | (SD) | (SD) | (SD)
--- | --- | --- | --- | --- | --- | --- | ---

CA1/CA2 | 27 | 32 | 25 | 21 | -6 | -36 | p = .88 | p = .04
(4) | (9) | (1) | (6) |

CA3 | 54 | 37 | 39 | 34 | -28 | -7 | p = .03 | p = .05
(11) | (11) | (3) | (7) |

CA4 | 21 | 13 | 15 | 12 | -28 | -4 | p = .003 | p = .05
(3) | (3) | (3) | (4) |

prosubiculum/ subiculum | 10 | 7 | 11 | 8 | +14 | +15 | p = .004 | p = .20
(2) | (1) | (2) | (2) |

presubiculum/ parasubiculum | 8 | 8 | 7 | 7 | -19 | -19 | p = .85 | p = .17
(3) | (2) | (.5) | (2) |

granular cell layer of dentate fascia | 18 | 23 | 14 | 15 | -20 | -32 | p = .31 | p = .07
(6) | (8) | (11) | (4) |

**Table 4a**: Absolute numbers of pyramidal cells (x 10^5).
For abbreviations see Table 3.
### Table 4b: Absolute numbers of glial cells (x 10^5).

For abbreviations see Table 3.

<table>
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<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>CA1/CA2</td>
<td>96 (16)</td>
<td>102 (29)</td>
<td>80 (4)</td>
<td>90 (20)</td>
</tr>
<tr>
<td>CA3</td>
<td>270 (60)</td>
<td>169 (21)</td>
<td>139 (25)</td>
<td>204 (31)</td>
</tr>
<tr>
<td>CA4</td>
<td>142 (24)</td>
<td>128 (35)</td>
<td>101 (41)</td>
<td>110 (26)</td>
</tr>
<tr>
<td>prosubiculum/ subiculum</td>
<td>94 (20)</td>
<td>66 (5)</td>
<td>71 (6)</td>
<td>80 (19)</td>
</tr>
<tr>
<td>presubiculum/ parasubiculum</td>
<td>148 (38)</td>
<td>113 (21)</td>
<td>73 (18)</td>
<td>122 (21)</td>
</tr>
<tr>
<td>Evaluated areas</td>
<td>Controls Males (n=7)</td>
<td>Controls Females (n=4)</td>
<td>Schizophrenics Males (n=2)</td>
<td>Schizophrenics Females (n=11)</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>CA1/CA2</td>
<td>63 (7)</td>
<td>49 (6)</td>
<td>59 (11)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>CA3</td>
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<td>50 (5)</td>
<td>75 (20)</td>
<td>52 (11)</td>
</tr>
<tr>
<td>CA4</td>
<td>47 (7)</td>
<td>31 (6)</td>
<td>50 (6)</td>
<td>39 (9)</td>
</tr>
<tr>
<td>prosubiculum/</td>
<td>44 (5)</td>
<td>34 (4)</td>
<td>45 (7)</td>
<td>41 (8)</td>
</tr>
<tr>
<td>subiculum</td>
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<td></td>
</tr>
<tr>
<td>presubiculum/</td>
<td>31 (8)</td>
<td>31 (2)</td>
<td>35 (11)</td>
<td>32 (5)</td>
</tr>
<tr>
<td>parasubiculum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>granular cell layer</td>
<td>204 (39)</td>
<td>198 (19)</td>
<td>210 (60)</td>
<td>222 (44)</td>
</tr>
<tr>
<td>of dentate fascia</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 5: Densities of pyramidal cells (x 100/mm³).
For abbreviations see Table 3.
Figure 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 6x) 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
Figures 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.

Figure 2: Hippocampal Segments CA 1 + CA 2
Figure 3: Hippocampal Segment CA 3

(x $10^6$)

- $25\%$ ns
- $35\%$ $p < .005$
- $20\%$ $p < .05$

- 48, $n=11$
- 36, $n=4$
- 39, $n=4$
- 31, $n=5$
Figure 4: Hippocampal Segment CA 4

(x 10^6)  c  cat  par  mixed

- 34%  p < .03
- 28%  p < .005
- 29%  p < .05
Figure 5: Subiculum

\[ x \times 10^6 \]

- c
- cat
- par
- mixed

- 8 n=11
- 9 n=4
- 13 n=4
- 7 n=5

+ 12% ns
- 19% ns
+ 12% ns
XI. 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 schizophrenics and 11 age-matched controls belonging to the Vogt-collection were determined.

Volumes of the whole hippocampal formation (p = .01), the whole pyramidal band (p = .001) and the hippocampal segments CA1/CA2 (p = .01), CA3 (p = .05), CA4 (p = .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 = .1).

The absolute number of pyramidal cells (tissue volume x cell density) was diminished in CA1/CA2 (p = .05), CA3 (p = .05) and CA4 (p = .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