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Hippocampal pyramidal cell disarray correlates negatively to cell number: implications for the pathogenesis of schizophrenia

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Abstract Brains from patients with therapy-refractory schizophrenia were examined with respect to pyramidal cell disarray in the hippocampus, a finding reported in some studies, but not confirmed in others. A significantly higher number of disarrayed cells was seen in the brains of the schizophrenic patients in all subfields of the Cornu Ammonis (CA) investigated. Compared with controls the schizophrenic patients also had significantly fewer pyramidal cells in the observed areas of CA1–CA3, but not in CA4. There were no signs of gliosis. Finally, there was a significant negative correlation between the number of disarrayed cells and the total number of pyramidal cells in CA1–3 in the group of probands and controls taken together, a finding interpreted as lending support to the idea of a prenatal migratory disturbance in the pathogenesis of schizophrenic syndromes.

Key words Schizophrenia · Hippocampus · Pyramidal cell count · Cell disarray · Migratory disturbance

Introduction

The hippocampal formation has attracted increasing attention in the research on schizophrenic syndromes since the 1970s. Findings indicating dysfunction in this region have been considered relevant since histopathologically well-described changes in the medial temporal lobe may be associated with symptoms resembling those in schizophrenic syndromes. In such patients imaging studies indicate that morphological changes are frequent in this region, especially in the left hemisphere [e.g. 62, 63]. The symptoms of temporal lobe epilepsy sometimes overlap those seen in schizophrenia as may the symptoms of lesions caused by tumors, traumas, or viral infections [23, 24, 43]. The classical findings that electrical stimulation of discrete cortical areas in this region during neurosurgery may evoke sensory distortions, hallucinations, and strong emotional reactions [33, 48] provide evidence that the medial temporal lobe is of relevance in the research on the pathophysiology of psychosis [41]. Furthermore, knowledge accumulated on the functional anatomy of the brain during recent years indicates that hippocampus and the closely connected entorhinal cortex are regions where converging polymodal sensory inputs are processed [44, 54]. From a theoretical point of view this suggests that facets of the phenomenology of schizophrenia may actually be explained by a dysfunction in this region. Besides projections via the dorsomedial thalamic nucleus and some direct fibers from the prefrontal cortex, the hippocampal pathway – CA1 of the Cornu Ammonis being a veritable bottleneck [65] – is an important connection between the higher mental functions of the cerebral cortex and the phylogenetically older hypothalamus, the center of drives and basal physiological functions [14, 51].

Memory impairment in schizophrenic patients, now unambiguously demonstrated by neuropsychological assessment, may partly be explained by a hippocampal disturbance [30, 32, 55, 56]. A sensory gating deficiency in schizophrenics, measured by the P50 wave of the auditory-evoked potential, is another relevant finding [1]. This deficiency is also assumed to facilitate simple conditioning. Neuropsychologically, these observations are in line with the increased sensitivity to stimuli seen in schizophrenics and their inability to focus attention. In a wider perspective a sensory gating deficiency has also been hypothesized to underlie such symptoms as hallucinations and delusions [28]. Facilitation of conditioning has been observed in animals with hippocampal lesions [49]. Recently, Knight has shown that event-related potentials and autonomic skin responses to novel stimuli are reduced in patients with hippocampal lesions [40]. Processing of novel stimuli engages a neural network also including the prefrontal and posterior parietal cortex, the former area

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also assumed to be involved in the pathophysiology of schizophrenia.

Post-mortem studies as well as structural and functional neuroimaging investigations provide further evidence that hippocampus is of importance in the pathophysiology of schizophrenia [15–19, for a review see 14]. Some findings have, however, not been replicated [5]. Hippocampal cell loss reported in some studies [26] has not been confirmed in other studies [12, 35]. In particular, the pyramidal cell disarray interpreted as a cell migratory disturbance of a prenatal origin, described in several studies emanating from Scheibel and coworkers [21, 22, 39, 58], has not been unambiguously confirmed [6] or has not been replicated at all [8, 12, 20, 35]. For this reason the brains of four male patients with therapy-refractory schizophrenia were examined with respect to hippocampal pyramidal cell orientation and cell number in the different sections of the Cornu Ammonis.

Materials and methods

Probands

The material consisted of brains from four male patients with therapy-refractory schizophrenia, though treated by neuroleptics for many years. All of them were cared for at the same ward for chronic patients. The following case histories are given:

1.Proband 1/408/79 (proband no/brain no/age at death). Born in 1915. Farm worker. First admission to hospital in 1938. Always considered shy. He never married. During the year of 1938 the patient experienced several episodes of acute psychosis with irritability, aggressiveness, anxiety, auditory hallucinosis, and ideas of being poisoned. He was in complete remission after the first two episodes, but after the third, in 1939, he never regained full mental health. Hospitalized from 1942. His state of health deteriorated in the late 1940s; he became gradually more aggressive. Lobotomized in 1950 and thereafter quiet, but gloomy. Always bizarre delusions and prominent rituals. Deceased in 1994. Cause of death: cardiac insufficiency. Diagnosis: catatonic schizophrenia, 295.2.

2.Proband 2/384/85. Born in 1909. Farm worker and later at work at a brickyard. Seems to have been ambitious, interested in literature, and attended evening courses in different subjects. Never married. In 1953 the patient was admitted to a mental hospital for the first time. He was aggressive, heard voices and was convinced that people were spying on him. Experienced himself as exposed to telepathy as well as electrical and magnetic fields. Despite neuroleptic treatment, he still heard voices, and he never gained insight into his delusions of influence and persecution. Deceased in 1994. Cause of death: bronchopneumonia. Diagnosis: paranoid schizophrenia, 295.3.

3.Proband 3/332/80. Born in 1913. Farm worker. Never married. Admitted to a mental hospital in 1941, described as very irritable and aggressive. He heard voices and had persecutory delusions. His affective repertoire was described as narrow, primitive, and blunted. Hallucinations became more and more prominent in his later years and he often argued with his voices which seemed to be predominantly evil. Deceased in 1993. Cause of death: cardiac infarction. Diagnosis: paranoid schizophrenia, 295.3.

4.Proband 4/302/81. Born in 1912. Farm worker and later a construction worker. Always considered gloomy and seems to have preferred to be by himself. Never married. For the first time mentally ill in 1939 with loss of interest and initiative, mutism, and motor retardation. Hospitalized, but in remission at discharge after a few months. Seems to have been largely symptom-free and at work until 1950. Then initially depressive and psychomotorically retarded. Prominent affective flattening, alogia, and avolition developed in the course of illness. The patient never regained mental health. Somatic and nihilistic delusions. He was very untidy and messed about with his feces. During the last decades of his life he stood on one leg for long periods each day and walked backwards. Deceased in 1993. Cause of death: pneumonia. Diagnosis: catatonic schizophrenia, 295.2.

A sister of the patient, deceased from tuberculosis in the early 1940s, was also mentally ill. According to the description in her record the symptomatology of the two siblings was similar.

Controls

The brains from eight age-matched male controls dying from non-cerebral diseases and without known mental illness were obtained as control cases from the Department of Pathology. These brains had been neurohistologically examined and no gross pathology had been detected. For details concerning the controls see Table 1.

Tissue handling

The brains were fixed in 4% formaldehyde, never later than 24 h post mortem. The brains were examined grossly and sectioned in 7 to 8-mm-thick coronal whole-brain slices which were scrutinized for morphological changes. Roughly every other brain slice was embedded in paraffin and sectioned at 5 μm, stained with hematoxylin and eosin, cresyl violet, and Luxol fast blue. When needed, supplementary pieces of the hippocampus were treated in the same way to provide comparable sections from midhippocampus in all cases. In a few cases additional stainings were performed with Gallyas and Campbells silver staining.

Morphometric analysis

All sections were coded and the morphometric studies were performed by one investigator with no access to diagnosis. The Cornu Ammonis (CA) sectors CA1–CA4 and the dentate gyrus were identified (Fig. 1). Since the border between CA2 and CA3 is diffuse and the validity of this subdivision has been questioned [35], the pyramidal cells of these two sectors were counted together as well as separately. The total number of pyramidal cells in the observed areas of the different CA sectors and granular cells of the dentate gyrus were determined using the Quantimet Q500 MC image analysis system (Leica Cambridge Ltd, Cambridge, UK). The orientation of the first consecutive 100 pyramidal cells counted from the centers of the CA1, CA2, and CA3 was measured directly on micrographs photographed in a Leica Aristoplan light microscope. Since it has been argued that disarray occurs most prominently at the interfaces between the ammonic subfields [21, 22, 39], it should be stressed that neurons were measured beginning from a point in the center of each such subfield in this study. Lines were drawn through each pyramidal cell reaching the ventricular margin perpendicularly. Pyramidal cell orientation was defined as the angle formed between this line and a second line along the axis

Table 1 Control subjects: causes of death

Case no/Brain no/ Age at death (years)	Causes of death
1/232/85	Cardiac infarction and pulmonary embolism
2/159/74	Aortic aneurysm rupture
3/621/72	Pancreatic cancer
4/274/81	Pulmonary embolism and ileus
5/248/85	Bronchopneumonia and cardiac insufficiency
6/689/82	Cardiac infarction and insufficiency
7/446/73	Cardiac infarction
8/467/60	Cardiac infarction

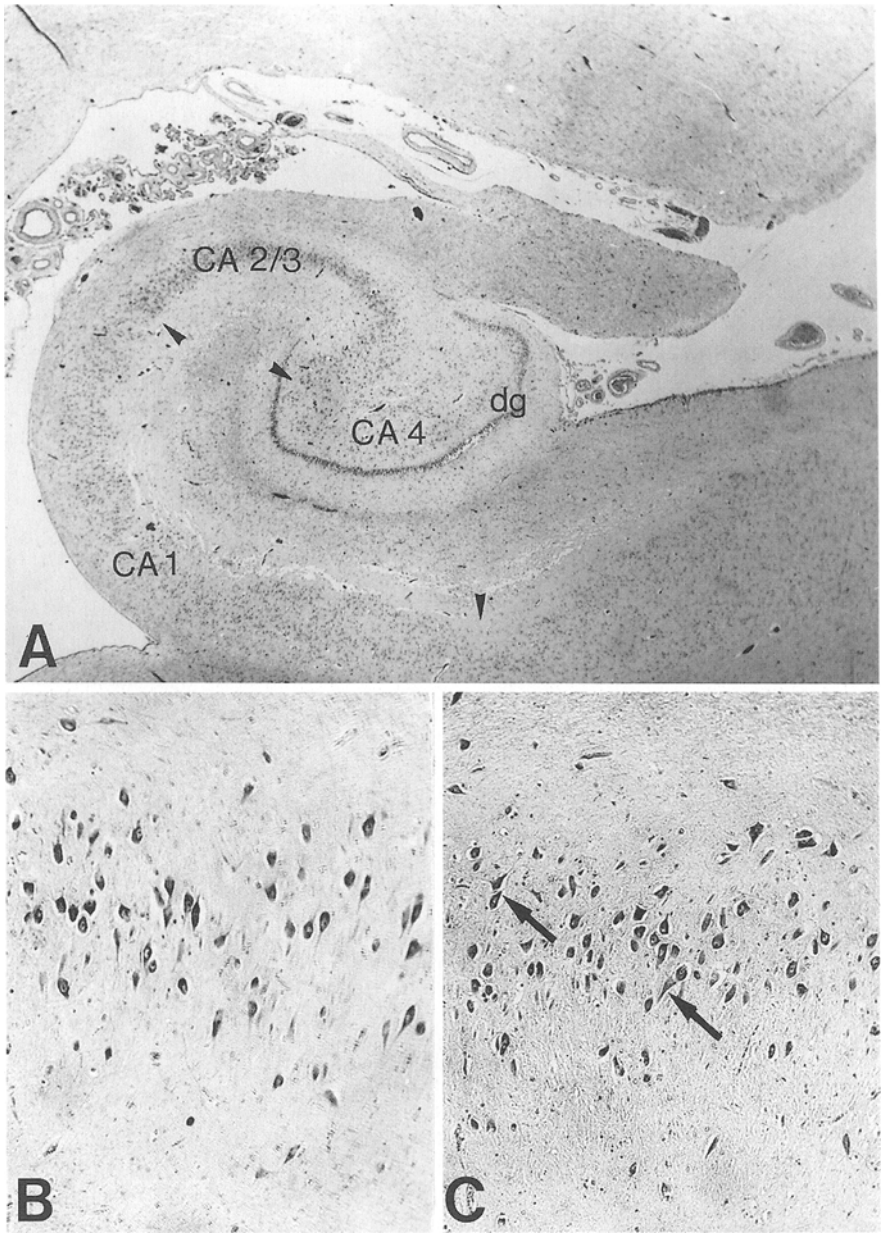

Fig. 1 A Section of the hippocampal formation showing the CA subdivisions and the dentate gyrus (*dg*). *Arrowheads* indicate the borders between subdivisions. Sections from the CA1 showing pyramidal cell orientation of **B** a control and **C** a schizophrenic patient. Note the higher degree of disarray in **C**. *Arrows* show disarrayed cells. **A** × 12.5. **B**, **C** × 150

of the pyramidal cell. Since disoriented cells are always present also in normal subjects, the criterion used was purely quantitative. The numbers of cells deviating more than 15, 25 and 35° from expected perpendicular position in the left hippocampal formation were determined.

Additionally, the glial cell number was counted in samples limited by the visual field of the microscope in each area observed. Different types of glial cells were not determined separately.

Statistics

Frequencies of disoriented cells in the samples containing 100 cells described above were compared by the Mann-Whitney U-test. In probands and controls taken together this figure approximates half of the total number of pyramidal cells in the observed areas of CA2 and CA3, but only a small fraction of the cells of CA1 which contains several thousand cells. Exact *P*-values were specified in each test. In correlation analysis Spearman's rank-order correlation was used.

Results

Gross and microscopic examination

In the control cases no pathological changes were disclosed but alterations pertaining to normal aging. Similar changes were noted in the brains of the probands. No signs of gross vascular diseases or tumors were detected. There were small infarctions in different areas of the cortex, as generally seen in elderly people, but not in the region here examined. In several probands changes as widened ventricles were seen, but in none of them were there signs of major age-related degenerative disease. One of the probands (4/302/81) had a congenital malformation, a mild cortical dysplasia of the frontobasal cortex on one side.

Table 2 Mean no. of glial cells per visual field (Mann-Whitney U-test; correction for ties)

Region	Schizophenic probands ($n = 4$)	Controls ($n = 8$)	Z	P
CA1	61.5 ± 8.4	77.4 ± 12.7	−1.87	n.s.
CA2	67.5 ± 16.4	68.5 ± 13.2	−0.60	n.s.
CA3	83.8 ± 16.4	93.5 ± 24.1	−1.11	n.s.
CA4	68.3 ± 16.2	79.0 ± 15.0	−1.11	n.s.

Table 3 Mean no. of pyramidal cells in CA1, CA2, CA3, CA2–3, and CA4 (Mann-Whitney U-test; correction for ties)

Region	Schizophrenic probands ($n = 4$)	Controls ($n = 8$)	Z	P
CA1	1329.3 ± 289.0	2271.1 ± 673.0	−2.38	0.0174
CA2	141.5 ± 29.6	260.6 ± 130.0	−2.21	0.0272
CA3	137.8 ± 36.8	237.0 ± 70.3	−2.38	0.0174
CA2–3	279.3 ± 55.2	497.6 ± 187.5	−2.55	0.0107
CA4	367.8 ± 55.9	427.0 ± 84.5	−1.28	n.s.

Table 4 Mean deviation from expected perpendicular position of 100 pyramidal cells in CA1, CA2 and CA3 (Mann-Whitney U-test; correction for ties)

Region	Probands ($n = 4$)	Controls ($n = 8$)	Z	P
A1	18.0° ± 2.5	8.8° ± 2.2	−2.73	0.0064
CA2	13.8° ± 1.0	8.1° ± 0.6	−2.74	0.0061
CA3	17.8° ± 2.2	9.0° ± 2.1	−2.73	0.0064

Glial and nerve cell count

The mean number of glial cells was lower in the schizophrenic probands in all four areas, CA1–CA4, but there were no significant differences (Table 2). The schizophrenic probands had significantly fewer pyramidal cells than the controls in the observed areas of CA1, CA2, CA3, and CA2–3, but not in CA4 (Table 3). There were no significant correlations with age in either group or the groups taken together.

As to the number of granular cells of the gyrus dentata, there was no difference in the observed areas between probands (mean 1964.8 ± 129.1) and controls (mean 1929.0 ± 267.1).

Pyramidal cell disarray

In the comparison between the four probands and eight controls the mean pyramidal cell deviations in respective sectors were significantly greater in the schizophrenics (Table 4). The pattern of disorientation was at random (Fig. 1 B, C).

The mean number of deviating cells in each region is shown in Table 5. Differences were significant in all areas with respect to all stipulated angles.

Correlation analysis

Since visual examination of figures indicated that there might be an association between the number of disoriented pyramidal cells and the total number of cells not limited to the group of probands but also in the group of controls, these two groups were pooled in a correlation analysis. Significant negative correlations could be demonstrated in all areas observed, though not with respect to all angles measured (Table 6).

Discussion

Neuron and glial cell number

The four probands in this study were old (mean age at death was 82 years). Although the probands and controls were matched with respect to age, objections may be raised that the findings reported herein are effects of age-related degenerative processes, pathological in character, or part of the normal aging of the brain. No signs of degenerative processes indicating organic dementia were observed at the pathological examination of the probands.

Table 5 Comparison by groups. Mean no. of pyramidal cells per 100 cells deviating more than 35, 25, and 15° in CA1, CA2, and CA3, and per 300 cells in CA1–CA3 (Mann-Whitney U-test; correction for ties)

Region and degree of deviation	Schizophrenic probands ($n = 4$)	Controls ($n = 8$)	Z	P
CA1 > 35°	13.5 ± 2.9	1.1 ± 0.8	−2.76	0.0058
CA1 > 25°	23.3 ± 6.3	4.0 ± 2.2	−2.73	0.0063
CA1 > 15°	40.3 ± 14.9	10.3 ± 4.4	−2.72	0.0065
CA2 > 35°	5.0 ± 0.8	0.6 ± 0.5	−2.84	0.0044
CA2 > 25°	13.8 ± 1.7	3.3 ± 1.3	−2.77	0.0056
CA2 > 15°	27.0 ± 4.5	8.1 ± 3.0	−2.72	0.0065
CA3 > 35°	11.0 ± 4.8	1.1 ± 1.0	−2.77	0.0056
CA3 > 25°	19.3 ± 1.3	5.4 ± 3.0	−2.73	0.0064
CA3 > 15°	39.8 ± 8.0	13.1 ± 5.1	−2.72	0.0066
CA1–3 > 35°	29.5 ± 7.2	2.9 ± 1.7	−2.74	0.0061
CA1–3 > 25°	56.3 ± 6.6	12.6 ± 5.9	−2.72	0.0066
CA1–3 > 15°	107.0 ± 18.8	31.5 ± 11.3	−2.72	0.0066

Table 6 Correlations between the no. of deviating cells per 100 cells and total no. of pyramidal cells in respective region (Spearman's rank-order correlation): schizophrenic probands and controls ($n = 12$)

Region and degree of deviation	r_s	P
CA1 > 35°	–0.785	0.002
CA1 > 25°	–0.678	0.015
CA1 > 15°	–0.753	0.005
CA2 > 35°	–0.644	0.024
CA2 > 25°	–0.553	n.s.
CA2 > 15°	–0.711	0.010
CA3 > 35°	–0.514	n.s.
CA3 > 25°	–0.758	0.004
CA3 > 15°	–0.685	0.014
CA1–3 > 35°	–0.751	0.005
CA1–3 > 25°	–0.734	0.007
CA1–3 > 15°	–0.776	0.003

Neither was there any excess of glial cells. (This latter finding is discussed below). It could be objected that the proband lobotomized in the 1950s was included. However, in a morphometric study on the hippocampus in schizophrenic patients two control groups were used, one of which included subjects lobotomized for reasons other than schizophrenia, such as, for example, chronic pain. There were no differences between the two control groups in the aspects relevant to our study [20].

According to a long-standing belief, seemingly established as a fact in a series of empirical investigations during the 1950s and 1960s, the number of neurons in the cerebral cortex steadily decreases during normal aging [19]. When, however, carefully excluding brains possibly affected by pathological processes, correcting for age-dependent differences in tissue shrinkage at preparation causing specimens from young subjects to shrink approximately 15% more than specimens from old subjects, thereby obviously affecting neuronal density measures [34], and, finally by introducing new stereological methods for the counting of neurons [67], negative correlations between age and the number of cortical neurons tend to disappear.

According to Terry et al. there seems to be a decrease in large pyramidal cells in the cerebral cortex and a concomitant increase in the number of small neurons [64]. Cell shrinkage as an effect of a decline in cell function, rather than cell death, may then be suggested to account for age-related neuropsychological changes such as normal memory impairment [9; see also 69, 70]. In a recent study of age-related changes in the human hippocampus no regional cell loss was found in the CA1 and CA2–3 areas or in the granular cell layer of the dentate gyrus, but there was a significant decrease in CA4 and the subiculum [68]. Essentially the same result, a non-significant age-related decrease in CA1–CA3 and a significant decrease in CA4, was obtained by Mani et al. in a non-stereological investigation [42]. Similarly, in an experimental setting, aged rats showing memory impairment did not have fewer neurons in the hippocampus than young rats [50].

A decrease in cell numbers, in terms of cell densities, has previously been reported [26, 37], although not confirmed by other studies determining total cell counts in coronal samples [12] or by applying stereological methods [35]. In the present study, there was no difference between probands and controls in the CA4 region – in which age-related changes in cell count have been observed [42, 68] – nor in the granular layer of the dentate gyrus. There was thus a selective and substantial loss confined to the CA1–3 regions.

Higher mean neuronal density has been reported in the posterior part of hippocampus compared with the anterior part [10]. Benes et al. [12] studied the posterior part and did not find a lower number of pyramidal cells in schizophrenics, but a non-significant though slightly higher number than in controls in three of four CA areas. Through analysing thicker sections, 20 instead of 5 μm as in the present study, the number of cells in the different areas was quite different in both schizophrenics and controls from those seen here. The pyramidal cells in Benes' schizophrenic and control subjects were conspicuously fewer in CA1 and more abundant in CA3 and CA4 [12]. The coronal-section plane used in this study is the one normally used for clinical pathological examination displaying midhippocampus.

The lack of gliosis found in this and most other studies [11, 52, 53, 59, 66], suggests that the difference in cell numbers is not an effect of pathological aging in comparison with controls. In this context it is well known that the Sommer sector (CA1–2) is sensitive to anoxia leading to gliosis. No such anoxic lesions were observed in this material.

Still, a few studies show increased gliosis in the hippocampal region of schizophrenic patients [60, 61], although excessive gliosis was found only in a minority of cases. In a stereological study on cell number in thalamus, nucleus accumbens, pallidum, and amygdala in brains of schizophrenics, Pakkenberg [46] found a significant reduction in neurons in mediodorsal thalamus and the ventromedial part of nucleus accumbens. Interestingly, there was also a concomitant significant reduction of glial cells [46]. In the present study, differences in glial cell number between probands and controls were never significant. There was, however, a reduction approximately proportional to the reduction in the number of pyramidal cells in all regions examined. The question whether there are postnatal pathological processes in the brain causing cell death without proliferation of reactive gliosis has been raised [25, 45] but should be regarded as controversial. A selective loss of perpendicularly oriented cells, increasing the proportion of disoriented cells, without concomitant gliosis seems, however, less probable.

Cell loss due to treatment with neuroleptic drugs may well be hypothesized. Pakkenberg, having demonstrated a significant reduction in nerve cells in the mediodorsal thalamus in patients treated with neuroleptics [46], in another study [47], compared the volume of this brain structure with brains from patients deceased in the preneuroleptic era. There was no significant volumetric differ-

ence between schizophrenic patients treated or not treated with neuroleptics, but again between these two groups and controls. There is, however, no experimental evidence that neuroleptic treatment would influence cell orientation.

Pyramidal cell disarray

It has strongly been argued that pyramidal cell disarray is of a prenatal origin [22, 57]. Disturbances in the cytoarchitectural organization of cell layers found in postnatal lesions appear quite different. In such cases there may either be a concomitant gliotic sclerosis or observable traits of a more heterogeneous "alien tissue" nature presumably more often of a prenatal than of an early postnatal origin [31]. Disorientation, caused by a focal lesion, is characterized, by a systematic deviation of cells in the same direction. This was certainly not the case in this study.

Pyramidal cell disarray in schizophrenic patients, demonstrated in the present study, has previously been reported, although several studies subsequently failed to replicate this observation [8, 12, 20, 35]. It could be argued that the degree of pyramidal cell disarray may be a trait associated with severity of illness. Scheibel's and Kovelman's original studies [39, 58] and the present study refer to chronic, therapy-refractory cases. In a later report [6] a relationship between the degree of cell disarray and behavioral impairment is suggested. A bimodal distribution of cases with respect to this parameter gives further support to this contention [21]. This study neither permits any conclusions whether there is a lower degree of neuronal disarray in cases less impaired nor whether paranoid schizophrenics have a higher degree of cell disorientation than other subtypes, the latter impression emanating from Kovelman and Scheibel [39].

There are indications that differences in the degree of cell disorganization between schizophrenic probands and controls are more pronounced in the middle and anterior part of the hippocampus than in the posterior part [39]. This may explain conflicting findings. In the aforementioned investigation by Benes et al. [12], not finding any difference in cell counts between schizophrenics and controls, the posterior part of hippocampus was examined. Neither was there any difference in cell orientation.

As with purely heterotopic pyramidal cells not reaching their destination, disorientation has been interpreted as a disturbance in cell migration and consequently of a prenatal origin [13, 22, 57]. "Migration" should be understood here in a wide sense also including the phase in brain ontogenesis, when the patterns of neural connectivity are being established [38]. Indications of a deficient cell migration in schizophrenics are not limited to the hippocampus. In the entorhinal cortex Jacob and Beckmann observed clusters of heterotopic α-cell in layer III (β layer), their proper final destination being layer II [36]. This finding has been confirmed in several other studies [7, 27]. A maldistribution of neurons between gray matter and the white matter subjacent to the cortical subpalate has been demonstrated in the frontal and temporal region by Akbarian and coworkers [2–4].

In the absence of postnatal signs of cell death, the low count of neurons observed in subcortical regions, such as thalamus and nucleus accumbens [46], might as well be interpreted as an effect of a cell migratory disturbance.

Conclusion

Against this background one should be cautious not to exaggerate findings in the hippocampus or to describe schizophrenia as a hippocampal disease. The effects of a migratory disturbance may plausibly be expressed diffusely all over the cerebral cortex. Even if migratory disturbance is limited to certain types of cells or a certain period of gestation, it would at least be present in wide regions of the nervous system. There are, however, several reasons why hippocampus is an appropriate brain structure to be studied in this context. Firstly, it is a cytoarchitecturally well-described area, where even discrete aberrations may be detected relatively easily. Secondly, hippocampus is a critical structure, where a small injury may give rise to large effects due to its relay resemblant function in the communication between different parts of the brain. A third reason is that there is a relevant phenomenological correspondence between symptoms seen in schizophrenia and independently established knowledge on localized neuropsychological function based on mapping of the effects of brain injury as well as of experimental lesions.

The negative correlation between total cell counts in the observed areas and the number of disoriented cells might perhaps reflect the combined effect of a migratory disturbance, causing cell disarray, an excess of cell death, and heterotopy during the migratory process. Possibly a high ratio of disarrayed cells/total number of cells is a general indication of migratory success. This negative correlation hints at the idea that there might be some critical threshold interval making a psychotic breakdown more probable when exceeded. It may be hypothesized that the vulnerability of pyramidal cells to migratory disturbance varies with their neurochemical character. A neurochemical characterization of disoriented cells is thus of obvious interest.

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