Recent Advances in the Neuropathology of Schizophrenia

by Bernhard Bogerts

Abstract

This article reviews some 50 neuroanatomical postmortem studies published in the last 20 years. The majority of these studies demonstrated various types of subtle anomalies in limbic structures, that is, the hippocampus, parahippocampal gyrus, entorhinal cortex, amygdala, cingulate gyrus, and septum of schizophrenia patients. A number of schizophrenic symptoms might be related to structural and functional disturbances of these brain regions. But these studies also reported subtle changes in parts of the basal ganglia, thalamus, cortex, corpus callosum, and brainstem neurotransmitter systems. Many of the studies, however, are based on small sample sizes and, therefore, must be regarded as preliminary. Cytoarchitectonic abnormalities and lack of gliosis in limbic structures as well as the absence of normal structural cerebral asymmetry in a substantial proportion of patients indicate that these structural anomalies may reflect a disorder of prenatal brain development and argue against the notion that schizophrenia is a progressive degenerative brain disorder.

The history of psychiatry has been, and continues to be, closely linked to the presence or absence of cerebral anatomical substrata for mental diseases. In the first half of the century, following Alzheimer's (1897) reports of neurohistological alterations in the cerebral cortex of patients suffering from dementia praecox, schizophrenia was the subject of some 200 pathoanatomical studies (David 1957). These studies were largely unsuccessful in consistently defining brain abnormalities in this disease. After several decades of neglect, interest in the neuropathology of schizophrenia has reemerged as one of the major challenges of current biological and psychiatric research.

The relationship between neuropathology and schizophrenia research is best reflected by the programs of the 11 international conferences on neuropathology that took place beginning in 1952. The topic was first included in the agenda in 1952 at the First International Congress of Neuropathology in Rome. The prevailing opinion at this conference was that the differences observed in the brains of schizophrenia patients were due to pre- or postmortem changes unrelated to the disease. After this conference, the topic disappeared from neuropathology meetings for nearly 40 years. Schizophrenia was next discussed internationally by neuropathologists at the 11th International Congress of Neuropathology in Kyoto in 1990. However, psychiatrists had become interested in the topic some years earlier. In 1985, at the 6th World Congress on Biological Psychiatry in Philadelphia, two psychiatrists organized the first international symposium since 1952 on the neuropathological aspects of schizophrenia. Since then the topic has appeared regularly at psychiatric congresses.

In the past many psychiatrists, psychologists, and neuroscientists assumed that schizophrenia was a

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disease of the mind rather than a disease of the brain because little was know about the neuroanatomy and physiology of brain systems involved in functions that are now thought to be disturbed in schizophrenia. Such brain functions comprise the coordination of cognitive and emotional activities, higher cortical integration and association of different sensory modalities, representation and analysis of environmental contexts, sensory gating, and the neuronal generation and control of basic drives and emotions. Increased knowledge in these fields of neuroscience (McLean 1952; Gray 1982; Mesulam 1986; Miller 1992) and a considerable number of brain-imaging and postmortem brain studies have shown that abnormal brain morphology and physiology are essential biological components of schizophrenia. This research provides compelling evidence that the disease is not mainly a result of psychosocial influences.

Methodological Problems of Neuropathological Studies in Schizophrenia

Much of the controversy over the neuropathology of schizophrenia was caused by methodological flaws associated with *qualitative* brain tissue assessment without morphometric-statistical evaluation. The application of qualitative brain tissue assessment—which is useful in describing obvious histological changes as seen in vascular, traumatic, infectious, toxic, and degenerative brain diseases—is problematic in defining subtle alterations in brain histology. Given the considerable variability of normal brain structure and the substantial overlap in neuroanatomy of schizophrenia patients and controls, the subtle abnormalities of macroscopic and microscopic brain anatomy presumed to underlie schizophrenia may be detectable only by applying optimal quantitative-morphometric, histological, and statistical procedures. Since these procedures were not available during the first half of the century when the early studies of psychiatric diseases were published, it is not surprising that only impressive morphological changes as seen in Alzheimer's, Pick's, and Parkinson's diseases were discovered previously.

If, as is widely believed, diagnostic constructs such as schizophrenia and affective disorders are composed of various clinical and biological subtypes, large samples of patients are necessary to obtain representative data by which subgroups can be characterized in terms of their brain morphology.

There are some critical reviews of the methods applied in anatomical postmortem research in schizophrenia (Jellinger 1985; Benes 1988; Pakkenberg and Gunderson 1988; Casanova and Kleinman 1990). Possible sources of error in these studies involve the following: brain changes secondary to complicating neurological or vascular diseases; preagonal conditions such as protracted coma; chronic diseases of peripheral organs; paraneoplastic limbic encephalopathia (Newman et al. 1990); drugs known to affect brain structures (e.g., cortisol, McEwen et al. 1992); time to fixation; and postmortem shrinkage and swelling of brain tissue. When quantifying smaller subcortical structures or cytoarchitectural cortical entities, thin serial sections are necessary to match exactly for the anatomical levels. This is especially important for the small limbic and phylogenetically old hypothalamic and brainstem structures as well as for the neurotransmitter- and peptide-containing cell groups, which are only a few millimeters wide.

Recent Neuropathological Findings in Schizophrenia

What follows is a review of the development of the neuropathological research in schizophrenia during the last 20 years. Several comprehensive reviews of earlier studies have been published (David 1957; Meyer 1963; Nieto and Escobar 1972; Jellinger 1985; Kirch and Weinberger 1986; Roberts and Crow 1987).

Brainstem Neurotransmitter Systems. Given the huge body of literature on cerebral neurotransmitters in schizophrenia, especially dopamine (DA), it is surprising that so few neurohistological studies of these cell groups have been performed.

Two studies that applied qualitative methods reported degenerative changes in the large cholinergic neurons of the basal nucleus of schizophrenia subjects (Buttlar-Brentano 1956; Averback 1981). A more recent quantitative study found normal cell numbers in the basal nucleus of schizophrenia patients (Arendt et al. 1983).

The lateral (nigrostriatal) and medial (mesolimbic) parts of the mesencephalic dopaminergic systems of six chronic schizophrenia subjects and six controls were evaluated by Bogerts et al. (1983*a*). There was a significant volume reduction (about 21%) of the lateral parts of the substantia nigra, and the the size of the nerve cell bodies was significantly reduced in the medial part (16%). Cell numbers were unchanged. The reduced cell size of the mesolimbic neurons was attributed to dopaminergic under-

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activity rather than overactivity of these cells.

Lohr and Jeste (1988) undertook volume measurements and cell counts in the noradrenergic locus ceruleus of 15 schizophrenic brains in the Yakovlev collection. They noted a trend for decreased locus ceruleus volume without loss of neurons, indicating a reduction of neuropil in the brains of schizophrenia patients compared to those of leucotomized controls. The results appeared comparable to those described in the substantia nigra by Bogerts et al. (1983*a*).

Investigating the brainstem reticular formation in four patients and five controls, Karson et al. (1991) found a twofold *increase* in the number of cholinergic neurons in the pedunculopontine nucleus and the dorsal tegmental nucleus as well as a reduced cell size in the locus ceruleus.

All these morphological studies of the brainstem neurotransmitter system are based on small sample sizes, and, therefore, must be regarded as preliminary. As of now, there are no histological studies of other neurotransmitter systems or the various neuropeptide-containing cell groups in the brainstems of schizophrenia patients.

Basal Ganglia. The frequency of schizophrenia-like symptoms in basal ganglia disorders such as Huntington's chorea and basal ganglia calcification (Davison and Bagley 1969) indicates that these brain regions may be significant in the pathophysiology of the disease.

Data from qualitative (Hopf 1954; Stevens 1982) and quantitative postmortem studies (Bogerts et al. 1986; Stevens 1986), along with blood flow and metabolism studies (Early et al. 1987; Luchins et al. 1989), support the notion that pallidum dysfunction might occur in catatonic schizophrenia. Catatonia is characterized by abnormal movements combined with positive and negative symptoms. The striatum and pallidum are regarded as parts of the extrapyramidal and limbic systems (Mesulam 1986) and are involved in the neuronal modulation of movement coordination. It is therefore conceivable that dysfunction of these brain parts plays a role in the pathogenesis of catatonic symptoms.

Unchanged volumes of the striatum and external pallidum but a subtle volume decrease in the internal pallidal segment were found in brains from the preneuroleptic era (Bogerts et al. 1985). Pallidal volume reduction was caused by a reduction in the catatonic subgroup (Bogerts et al. 1986; Stevens 1986). In the same series of brains, catatonic patients had a decreased diameter of the microneurons in the striatum (Dom et al. 1981). However, a study of patients chronically treated with neuroleptics found bilaterally *increased* striatal volumes, which reached a significant level on the left side (Heckers et al. 1991*a*). Remarkably, two magnetic resonance imaging (MRI) studies also found larger striatal volumes or cross-sectional areas in chronically treated schizophrenia patients (Jernigan et al. 1991; Swayze et al. 1992).

One possible explanation for an increased striatum in chronically neuroleptic-treated patients is that neuroleptics cause a functional hyperactivity of the striatum because they block inhibitory dopaminergic input and, thus, could lead to an activation hypertrophia of the striatum.

Thalamus. Cell loss and reduced tissue volume of medial thalamic structures were described several decades ago in brains of schizophrenia patients in the Vogt collection (Fünfgeld 1925; Bäumer 1954; Treff and Hempel 1958). To our knowledge, the Treff and Hempel study (1958) was the first to apply modern morphometric-statistical procedures to determine cell densities in schizophrenic brains. The authors described a significant reduction of neurons in the mediodorsal nucleus of the thalamus of five catatonic and three paranoid patients as compared to eight controls. Similar results were published by Pakkenberg (1990). Dom et al. (1981) reported a significant reduction of microneuron densities in the pulvinar of the thalamus.

In one planimetric study, volumes of all large subnuclei of the thalamus were determined (Lesch and Bogerts 1984). No differences relative to the controls were found, with the exception of a significant reduction of the periventricular gray matter surrounding the third ventricle.

If thalamic dysfunction caused schizophrenia-like symptoms, as assumed by some authors (Huber 1957; Gross and Huber 1972), such a symptomatology might be expected in patients with known diseases of the thalamus. The extensive literature on organic lesions of the thalamus and the diencephalon describes clinical symptoms such as apathy, drowsiness, mental lethargy, stuporous conditions, and disturbances of memory, and sensory phenomena such as hypesthesia, hyperpathia, and painful perceptions as being most characteristic (for a review, see Lesch and Bogerts 1984). Positive psychotic symptoms usually do not occur. Thus, clinical symptoms associated with dysfunction of the thalamus resemble the negative symptoms of schizophrenia. This

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assumption is supported by the observation that in computed tomography (CT) scans of schizophrenia patients, third ventricular enlargement (possibly indicating atrophy of the surrounding thalamus) occurs in patients with chronic negative symptoms (Gross et al. 1982).

Corpus Callosum. Structural anomalies of the midline area of the corpus callosum were demonstrated by several MRI scan and postmortem studies (Rosenthal and Bigelow 1972; Bigelow et al. 1983; Mathew and Partain 1985; Nasrallah et al. 1986; Uematso and Kaiya 1988; Günther et al. 1989; Rossi et al. 1989; Raine et al. 1990). The findings, however, are inconsistent, with reports of increased (Rosenthal and Bigelow 1972) as well as decreased (Rossi et al. 1989) midline areas. MRI studies reporting shape abnormalities are more consistent. Sex differences in anterior and posterior callosal thickness in normal controls seem to be reversed in schizophrenia subjects (Nasrallah et al. 1986; Raine et al. 1990), and the mean curvature in the corpus callosum is more marked in this group (Casanova et al. 1991).

Cortex. Nearly 100 years ago, Alzheimer (1897) described pallor and loss of pyramidal cells in the cortex of patients with dementia praecox. Some years later, Southard (1915) reported atrophy, mainly in the cortical association centers. Some 40 years ago, the Vogts (1948, 1953) qualitatively described cell gaps and so-called dwarf cells in the cerebral cortex of schizophrenia patients that later were regarded as histological artifacts (Peters 1967).

Studies using regional cerebral blood flow (rCBF), positron emission tomography (PET), and single photon emission computed tomography (SPECT) have reported reduced frontal activity in chronic schizophrenia patients (Ingvar and Franzen 1974; Buchsbaum et al. 1982, 1984; Weinberger et al. 1986). This research has prompted interest in cortical dysfunctions in schizophrenia.

Although the literature contains many perfusion studies of cortical regions in schizophrenia, very few histopathological studies of the cortex have been performed in the new era of neuropathological schizophrenia research.

Colon (1972) reported a reduction of cortical thickness and cell loss in deep cortical layers in three senile schizophrenia patients. Two studies showed lower neuronal densities and deficits in small interneurons in the prefrontal cortex and anterior cingulate gyrus (Benes et al. 1986, 1991*a*).

Three planimetric postmortem studies of the whole cortex have been performed. One reported significant reductions of cortical volume (12%) and central gray matter (6%) in schizophrenia patients (Pakkenberg 1987). The two other studies reported virtually identical volumes of cortex, white matter, and whole hemispheres in patients and control subjects (Rosenthal and Bigelow 1972; Heckers et al. 1991*b*).

Pathology of the frontal cortex might well explain some psychopathological aspects of schizophrenia, namely negative symptoms and cognitive deficits. Frontal lobe syndromes caused by brain tumors, injuries, lobotomy, or Pick's disease are characterized by apathy, loss of drive, inappropriate affect, social withdrawal or disinhibition, poor judgment, and psychomotor retardation (Fuster 1989). Many of these symptoms are commonly seen in patients with negative schizophrenia.

Limbic Structures. Since the first report of reduced tissue volume in temporolimbic structures of schizophrenia patients 10 years ago (Bogerts et al. 1983*b*), some 30 quantitative or qualitative anatomical postmortem studies in limbic structures of schizophrenia subjects have been published. Subtle structural changes in at least one of the investigated regions were found in 25 of these studies (Bogerts 1984; Kovelman and Scheibel 1984; Bogerts et al. 1985, 1990*c*; Brown et al. 1986; Falkai and Bogerts 1986, 1989; Jakob and Beckmann 1986; Altshuler et al. 1987, 1990; Benes and Bird 1987; Benes et al. 1987, 1991*a*, 1991*b*; Colter et al. 1987; Falkai et al. 1988*a*, 1992; Crow et al. 1989; Jeste and Lohr 1989; Arnold et al. 1991; Beckmann and Jakob 1991; Casanova et al. 1991; Conrad et al. 1991; Heckers et al. 1991*a*; Falkai et al., in press). Three studies reported no structural changes (Christison et al. 1989; Heckers et al. 1990*a*, 1990*b*).

The findings in limbic brain regions include the following:

1. Reduced volumes of cross-sectional areas of the hippocampus, amygdala, parahippocampal gyrus (Bogerts 1984; Bogerts et al. 1985; 1990*c*; Brown et al. 1986; Falkai and Bogerts 1986; Colter et al. 1987; Falkai et al. 1988*a*; Jeste and Lohr 1989; Altshuler et al. 1990), which were later corroborated by morphometric MRI studies of mesiotemporal structures (DeLisi et al. 1988; Suddath et al. 1989, 1990; Barta et al. 1990; Becker et al. 1990; Bogerts et al. 1990*a*; Dauphinais et al. 1990; Rossi et al. 1990; Jernigan et al. 1991; Shenton et al. 1992).

2. Left temporal horn enlargement, which is consistent with tissue

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loss in the surrounding limbic structures (Bogerts et al. 1985; Brown et al. 1986; Crow et al. 1989; Heckers et al. 1990*b*).

3. Reduced cell numbers or cell size in hippocampus or parahippocampal gyrus or entorhinal cortex (Falkai and Bogerts 1986; Jakob and Beckmann 1986; Falkai et al. 1988*a*; Jeste and Lohr 1989; Benes et al. 1991*b*; Casanova et al. 1991).

4. White matter reductions in parahippocampal gyrus or hippocampus (Colter et al. 1987; Heckers et al. 1991*a*).

5. Disturbed architecture and abnormal cell arrangements in the hippocampus, and entorhinal and cingulate cortex (Kovelman and Scheibel 1984; Jakob and Beckmann 1986; Benes and Bird 1987; Falkai and Bogerts 1989; Arnold et al. 1991; Conrad et al. 1991; Falkai et al., in press).

6. Increased vertical axon numbers and deficits in small interneurons in the cingulate gyrus (Benes and Bird 1987; Benes et al. 1991*a*).

7. Increased incidence of a cavum septi pellucidi (Degreef et al. 1992*b*).

Two groups could not confirm the finding of cellular disarray in the hippocampus (Christison et al. 1989; Benes et al. 1991*b*), and one group could not find significant volume and cell number reductions in the hippocampus and the entorhinal cortex (Heckers et al. 1990*a*, 1990*b*, 1991*a*).

Although the type and extent of the reported limbic system pathology in schizophrenia vary, and although there seems not to be a homogeneous pattern of limbic pathology in schizophrenia, the vast majority of authors agree that there are subtle changes in limbic brain regions in a significant percentage of schizophrenia subjects. The magnitude of the pathology is far less than that seen in the known degenerative brain diseases. Limbic tissue volumes and cell numbers and size differ by some 10 to 30 percent between schizophrenia patients and control subjects, and there is considerable overlap between patients and controls. About 25 percent of the patients have values outside the range of the controls.

A common principle in all neurodegenerative or hypoplastic brain disorders is that reduced volumes and cell numbers as well as cytoarchitectural abnormalities reflect disturbed function or a reduced functional capacity of the affected structure. If the same principle can be applied to schizophrenia, it is reasonable to conclude that limbic system pathology is an essential component of the pathophysiology of the disease.

Our present knowledge of brain anatomy and physiology allows an attempt to relate limbic dysfunction to a broad spectrum of schizophrenic symptoms. The limbic and paralimbic brain regions, such as the hippocampus, amygdala, parahippocampal gyrus, entorhinal cortex, cingulate gyrus, orbital cortex, and temporal pole, should be regarded as highly organized supramodal association and integration areas (Jones and Powell 1970; Swanson 1983; Mesulam 1986; Schmajuk 1987; Miller 1992). It seems reasonable to assume that structural and functional deficits in these brain regions are associated with the problems experienced by many schizophrenia patients in the higher integrative and associative brain functions. These problems lead to distorted interpretations of reality (Stevens 1973; Torrey and Peterson 1974; Bogerts 1987, 1989, 1990). All sensory information finally converges in the hippocampus and the amygdala, which are key structures in sensory information processing (van Hoesen 1982), context analysis (Miller 1992), sensory gating, and the comparison of present with past experience (Gray 1982). Furthermore, the amygdala and the hippocampus control the phylogenetically old basic drives and emotions that are generated in neuronal networks of the septum hypothalamus complex. Thus, in addition to disturbed sensory-information processing, limbic pathology could also explain the dyscontrol syndrome of basic drives and emotions that is frequently seen in schizophrenia patients (Bogerts 1985, 1989; Bogerts and Falkai 1991).

Since the amygdala and the hippocampus (and to some extent the orbital cortex) link the neocortical association areas with the septum-hypothalamus complex, and since there are no direct connections between the neocortex and the hypothalamus (Palkovits and Zaborsky 1979; Swanson 1983), structural and functional disturbances of these key limbic regions must lead to a dissociation between neocortical-cognitive activities and hypothalamic-emotional reactions to these activities. This dissociation between cognition and emotion is one of the core symptoms of the patients and led Bleuler (1911/1950) to coin the term "schizophrenia."

Autopsy reports of organic brain diseases mimicking schizophrenia provide additional support for the assumption that temporolimbic pathology can cause schizophrenia-like symptoms. In the initial stages of the disease, viral infections with high affinity for the medial temporal lobe (e.g., herpes simplex encephalitis, rabies) often produce severe emotional symptoms of fear, aggression, anxiety, irritability, periods of apathy or restlessness,

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overattention to external stimuli, distractibility, inappropriate sexual behavior, and even paranoid symptoms and hallucinations (Glaser and Pincus 1969; Himmelhoch et al. 1970; Greenwood et al. 1983). The same symptoms can be caused by medial temporal lobe tumors, infarctions, and traumas (Hillbom 1951; Mulder and Daly 1952; Malamud 1967; Davison and Bagley 1969), and temporal lobe epilepsy (Slater et al. 1963; Sherwin 1982), especially if the lesion is on the left side and originated in the fetus or perinatally (Flor-Henry 1969; Roberts et al. 1990). Permanent psychotic behavior with unsociability and hostility also has been described in epilepsies originating in the cingulate gyrus (Mazars 1970), which is functionally closely connected with the temporolimbic structures. At least in the initial stages, such organic brain diseases affecting the limbic system are frequently misdiagnosed as schizophrenia.

Direct evidence linking temporolimbic pathology to schizophrenic symptoms was provided by brain imaging studies using CT (McCarley et al. 1989; Bogerts et al. 1991), MRI (Besson et al. 1987; Bogerts et al. 1992; Degreef et al. 1992*a*), and PET (DeLisi et al. 1989; Kawasaki et al. 1992; Liddle et al. 1992). According to these studies, there is a particularly strong association between left temporolimbic pathology and the positive symptoms of schizophrenia.

Brain Size and Weight. Results of postmortem studies of brain weight and size are inconsistent. Some early, poorly controlled studies did not find cerebral atrophy or reduced brain weight (Broser 1949), while others qualitatively described cerebral atrophy in a significant proportion of patients (Jellinger 1980, 1985). More recently, three controlled quantitative studies found significant decreases in brain weight (5%–8%) (Brown et al. 1986; Pakkenberg 1987; Bruton et al. 1990) and significant reductions (4%) of brain anterior-posterior length (Bruton et al. 1990). One study found nearly identical brain weight and hemispheric volumes in schizophrenia patients and control subjects (Heckers et al. 1991*b*).

Studies on the Etiology of the Disease

Several neuropathological strategies may be used to study the etiology of schizophrenia, including investigation of glial cells, examination of cortical architecture, and studies of cerebral structural asymmetry.

Investigation of Glial Cells. Cell body and fiber densities of the reactive glial cells are important indicators of the nature of tissue volume or nerve cell loss. Ongoing and progressive diseases, infections, and other acute brain lesions are accompanied by a tissue repair response. This response results from astrocytes developing hyperplasia and proliferations of cell bodies and fibers (Friede 1989; Casanova 1991; Stevens 1991). The immature brain is not capable of reactive gliosis (Friede 1989). If the structural anomalies reflect developmental disturbances, perinatal complications, or inherited variations, one would not expect gliosis, since only pathological events occurring after the second trimester of pregnancy (e.g., viral infections, hypoxia, or atrophic processes) are associated with astrocytic reaction (Larroche 1984; Oyanagi et al. 1986). Therefore, absence of gliosis in a structurally changed brain region is compatible with a fixed, very early prenatal or genetic pathology. An earlier gliotic response to a perinatal lesion may disappear many years after the initial lesion (Casanova 1991; Stevens 1991).

Gliosis has been described qualitatively in periventricular and temporolimbic structures (Nieto and Escobar 1972; Stevens 1982; Bruton et al. 1990), brainstem (Fisman 1975), and corpus callosum (Nasrallah et al. 1983). The major problem with these qualitative studies of gliosis is that they do not allow a quantitative-statistical comparison of glial cell densities.

Ten controlled quantitative studies found no evidence of gliosis in the medial temporal lobe, cingulate gyrus, or mediodorsal nucleus of the thalamus (Benes et al. 1986, 1991*a*; Falkai and Bogerts 1986; Roberts et al. 1986, 1987; Casanova et al. 1987; Falkai et al. 1988*a*; Stevens et al. 1988; Crow et al. 1989; Pakkenberg 1990). However, cell loss, reduced volumes, and cytoarchitectonic changes occurred in the same regions.

It is possible that in some of these studies the applied densitometric methods for assessing glial fibrillary acidic protein (GFAP) levels were not sensitive enough to detect moderate degrees of gliosis (Casanova et al. 1987; Stevens et al. 1988; Stevens 1991). Moreover, all of these quantitative studies investigated relatively small samples in which moderate gliosis, if any, would not have been detected by the applied statistical tests in subgroups of patients.

In a recent preliminary morphometric study in which GFAP-stained astrocytes were counted, a subtle but significant increase in astrocyte cell bodies was found around the third ventricle (Bogerts et al. 1990*b*).

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As a group, the glial cell studies seem to indicate that the anatomical abnormalities described in the mesiotemporal structures, cingulate gyrus, and thalamus are not associated with gliosis and, therefore, might reflect a disorder of brain development. There might, however, also be a subgroup of patients with a reactive gliosis around the third ventricle, possibly caused by a subtle brain lesion suffered later on.

Examination of Cortical Architecture. Abnormal architectonic arrangements of single nerve cells, cell clusters, or cortical layers are strong indicators of disturbed early brain development.

Cytoarchitectural anomalies in the brains of schizophrenia subjects were described in the dentate gyrus (McLardy 1974) and cornu Ammonis (CA) segments of the hippocampal formation (Scheibel and Kovelman 1981; Kovelman and Scheibel 1984; Conrad et al. 1991), in the frontal cortex and cingulate gyrus (Benes et al. 1986; Benes and Bird 1987), and in the entorhinal cortex (Jakob and Beckmann 1986; Falkai et al. 1988*b*, in press; Falkai and Bogerts 1989; Arnold et al. 1991).

The reported cytoarchitectural abnormalities are subtle and not nearly as extensive as the well-known disorders of cortical development, that is, classical lissencephaly, Miller-Dieker syndrome, Walker-Warburg malformation, and developmental dyslexia (Bogerts and Falkai 1991). It has recently been shown that abnormally positioned prealpha cell clusters in the entorhinal cortex not only occur in schizophrenia patients but also in a substantial proportion of nonpsychiatric controls. However, abnormal clusters were found significantly more frequently in the left hemisphere of the schizophrenia patients (Falkai et al., in press).

A more obvious sign of abnormal brain development in schizophrenia is an increased prevalence of the cavum septi pellucidi in postmortem brains and MRI scans of schizophrenia patients (Degreef et al. 1992*b*). In fetuses, the two layers of the septum pellucidum are separated by a cavity that begins to shrink before birth and disappears long before adulthood (Shaw and Alvord 1969). The cavum remains in only a small percentage of adults. However, according to Degreef et al. (1992*b*), postmortem brains of schizophrenia patients show a more than twofold increase in prevalence of cavum retention, and MRI scans of schizophrenia patients show a tenfold increase.

Studies of Cerebral Structural Asymmetry. The normal structural asymmetry of the brain includes larger left planum temporale, longer left Sylvian fissure, and larger right frontal and temporal lobes (Geschwind and Levitsky 1968; Galaburda et al. 1987). These asymmetries develop in the second and third trimesters of pregnancy (Witelson and Pallie 1973; Wada et al. 1975; Wada and Davies 1977). Some evidence now indicates that this normal cerebral asymmetry is reduced, absent, or reversed in left-handed persons (Steinmetz et al. 1991) and those with dyslexia (Galaburda et al. 1985).

Although several CT (Andreasen et al. 1982; Luchins et al. 1982) and MRI studies (Johnstone et al. 1989; Bogerts et al. 1990*a*) suggest that the normal structural asymmetry is absent in schizophrenia patients, this anomaly only very recently became a topic of neuropathological studies of psychiatric diseases (Crow et al. 1989; Crow 1990; Bilder and Degreef 1991; Falkai et al. 1992).

Most of the above-mentioned postmortem studies did not deal with left/right differences. Some, however, did report selective left temporal horn enlargement (Brown et al. 1986; Crow et al. 1989) or a tendency toward left but not right ventricular enlargement (Heckers et al. 1990*b*). Cytoarchitectural abnormalities are reported to be more severe in the left than in the right entorhinal cortex (Jakob and Beckmann 1986; Falkai et al., in press).

Crow (1990) postulated that schizophrenia was caused by a developmental anomaly of cerebral asymmetry and suggested that temporal lobe asymmetries provide an important key to the etiology of the disease. This view has gained further support from the recent reports of an absence of normal Sylvian fissure asymmetry in schizophrenia patients (Crow et al. 1992; Falkai et al. 1992).

Comment

The classical era of neuropathological schizophrenia research failed to demonstrate convincingly that the brains of schizophrenia patients had anatomical anomalies. However, further research on schizophrenia has received a strong impetus from modern neuroimaging studies. This article has reviewed some 50 neuroanatomical postmortem studies in schizophrenia published over the last 20 years. The majority of these studies demonstrated various types of subtle anomalies in the limbic structures of schizophrenia subjects, that is, hippocampus, parahippocampal gyrus, entorhinal cortex, amygdala, cingulate gyrus, and septum. A broad spectrum of schizophrenic symptoms might be related to structural and functional disturbances of these limbic brain

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regions. Because the functional significance of the limbic system was unknown until recently (McLean 1952), these brain regions were overlooked in the first half of the century.

There is as yet no evidence of a specific and homogeneous pathological substratum characteristic common to all patients diagnosed with schizophrenia. Some authors found abnormalities in the brainstem transmitter systems, thalamus, basal ganglia, corpus callosum, and cortex. At this point, we do not know whether these abnormalities occur in the same or different patients. To answer this, all brain regions and parameters of interest have to be evaluated and then statistically intercorrelated in large samples of patients and controls. This is a very time consuming but important task for future research.

The pathomorphological changes in schizophrenia are subtle and not comparable in magnitude to the brain tissue loss seen in the well-known degenerative brain disorders. The changes cannot be seen in all schizophrenia patients. There is a considerable overlap between patients and healthy controls, and morphometrically only a minority (20%–30%) have values below the range of matched healthy control cases. An additional difference from the neurodegenerative disorders is that, at least in most patients, the structural changes are not progressive and probably were acquired very early in life (Weinberger 1987; Bogerts 1989; Crow 1990; Benes et al. 1991*a*; Bogerts and Falkai 1991; Jones and Murray 1991; Roberts 1991).

In a recent review (Bogerts and Lieberman, in press), we categorized the recent postmortem studies in schizophrenia. In 27 studies the findings were consistent with a disorder of brain development, in 8 studies results were consistent with an inflammatory or degenerative brain disease, and in 14 studies there was no comment on the etiology of the disease. Thus, the majority of studies agree that at least a significant proportion of patients suffer from a subtle disorder of early brain development.

This conclusion is consistent with a number of studies showing that infants at risk for schizophrenia suffer from signs of neurointegrative defects and pandysmaturation (for a review, see Fish et al. 1992), and with observations of an increased incidence of minor physical abnormalies in the patients (Waddington et al. 1990).

A developmental defect alone cannot explain the course of the disease that is characterized by onset of the typical schizophrenic symptoms in early adulthood, relapses and recoveries, and the exacerbation of symptoms under stress. Several theories offer an explanation for the long latency between the early disturbance of brain development and the onset of the typical clinical symptoms (Bogerts 1987, 1989; Weinberger 1987; Murray et al. 1988; Stevens 1992). The common factor in all these theories is that they regard the structural abnormalities in brains of schizophrenia patients as vulnerability markers that predispose the brain to decompensation during stress and during the vulnerable age period between puberty and old age.

Proposed additional factors are late myelination in the frontal or entorhinal cortex (Weinberger 1987; Benes 1989), gonadal and corticosteroid hormones (Bogerts 1987, 1989), abnormal synaptic sprouting (Stevens 1992), or psychosocial stressors (Zubin and Spring 1977), thus developing the typical clinical pictures of schizophrenia.

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