The Temporolimbic System Theory of Positive Schizophrenic Symptoms

by Bernhard Bogerts

Abstract

This article proposes that subtle structural and functional disturbance of limbic key structures in the medial temporal lobe—especially of the left hippocampal formation and parahippocampal gyrus—can explain the so-called positive symptoms of schizophrenia. After presenting pathophysiological considerations linking limbic dysfunction to schizophrenia, the article reviews evidence from structural, biochemical, and functional studies supporting the theory. Also discussed here are neurodevelopmental and laterality aspects, as well as predictions, questions, and future tasks derived from the theory.

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One of the most famous patients in European psychiatry and the best example for the classic concept of paranoia was teacher Ernst Wagner. His case can be taken as representative of the long-lasting debate on psychodynamic versus biological causes of paranoid symptoms. Wagner was a respected and successful teacher in a village near Stuttgart, Germany. In 1913, at age 38, he stabbed his wife and four children, shot and killed eight members of his village, wounded 12 others, and burned down several buildings. Later psychiatric examination revealed that he suffered from long-lasting, severe persecution ideas that finally led him to kill his supposed enemies.

Leading psychiatrists (e.g., Kraepelin [1899], Bleuler [1911/1950], Schneider [1959]), who during that time developed our present concepts of schizophrenia, debated Wagner's case; Gaupp (1938), who published it, and Kraepelin diagnosed Wagner as suffering from "paranoia." According to their concept (Kraepelin 1899; Gaupp 1938), paranoia was defined as an abnormal but psychologically understandable development caused in predisposed personalities by crucial life events (Wagner practiced sodomy 12 years before the mass murders; since then he had felt persecuted). Paranoia further was charac-

terized by the absence of any intellectual impairment—the essential difference from Kraepelin's view of dementia praecox.

In contrast, Kurt Schneider and his school diagnosed Wagner as having a subtype of schizophrenia and postulated a biological brain disease as the cause for Wagner's psychotic symptoms (Janzarik 1949).

The yet-unsolved historic controversy between the psychological and biological concepts of Wagner's paranoid psychosis was recently supplemented by an unexpected discovery: His brain was found in the Vogt collection in Düsseldorf, Germany. Surprisingly, the well-preserved and stained serial sections had never been examined. Wagner had a clear developmental abnormality in a limbic key structure: In the left posterior parahippocampal cortex was a distinct invagination clearly indicating a regionalized disruption of limbic cortical development. Otherwise, the brain looked normal; there was especially no ventricular enlargement and no cortical atrophy. A detailed description of Wagner's life and of the neuropathological finding is published in Bogerts (1997).

The Theory

Wagner's case can be taken as the most prominent historic example presented here for the theory of paranoid schizophrenia. According to that theory, small structural and functional disturbances of limbic key structures in the medial temporal lobe—especially of the left hippocampal formation and parahippocampal gyrus—play a major role in the pathophysiology of the so-called positive symptoms of schizophrenia: paranoid ideas, delusions, and thought disorder.

The theory does not challenge the view that different types of brain pathology may underlie the broad spectrum

of clinical symptoms seen in schizophrenia patients, and that the neurophysiological correlates of the schizophrenias may be distributed over extensive brain regions. There is evidence for structural and functional changes outside the limbic system—for example, in the thalamus, basal ganglia, and prefrontal cortex (for a review, see Bogerts 1993; Shapiro 1993; Chua and McKenna 1995). It is conceivable that negative symptoms—especially intellectual impairment and cognitive deficits, autism, loss of drive, anhedonia, and emotional flattening—may be caused by a more generalized and bilateral brain pathology affecting such areas as the amygdala; the frontal, temporal, and parietal cortical association areas; or the thalamic regions. Catatonia might be related to a basal ganglia disorder.

It is beyond the scope of this article to discuss involvement of the other brain structures in the broad spectrum of schizophrenia symptomatology; the article focuses on positive symptoms, especially on paranoid schizophrenia and the proposed association to temporolimbic pathology.

More than 20 years ago, Stevens (1973) and Torrey and Peterson (1974) postulated that schizophrenia may be linked to dysfunction of limbic structures. Influenced by their work, my colleagues and I started neuropathological studies in limbic and other structures of schizophrenia patients; later we offered an explanation for the close association between temporolimbic pathology found in the patients and some symptoms of this disorder (Bogerts 1985, 1989, 1991, 1993).

The core of the theory presented here is that limbic dysfunction causes a dissociation between higher neocortical cognitive activities and the phylogenetically older brain areas linked to basic drives and emotions. Dissociation between cognition and basic emotions is, according to Bleuler (1911/1950), a primary symptom of the "group of schizophrenias."

The theory is essentially based on findings of structural and functional alterations in the limbic system, and on knowledge of the anatomy of afferent and efferent connections of the temporolimbic structures with neocortical association areas, the hypothalamus, and the brainstem.

Anatomical and Pathophysiological Considerations

It is now well known that all sensory information from the external world—after passing unimodal and polymodal cortical association areas—finally converges in the hippocampus and amygdala. They are regarded as key structures in sensory-information processing (van Hoesen 1982; Mesulam 1986), context analysis (Millner 1992),

sensory gating, and the comparison of present with past experience (Gray 1982). Hippocampus, amygdala, entorhinal cortex, and the structures closely related to them (such as cingulate gyrus, orbital cortex, and temporal pole and prefrontal cortex) are to be regarded as supramodal association and sensory-integration areas (Jones and Powell 1970; Swanson 1983; Mesulam 1986; Schmajuk 1987; Millner 1992).

Recently, there was a proposal that the hippocampus and related medial temporal lobe memory system are essential for learning of relations among various exteroceptive sensory stimuli and of relations among contextual cues, while the amygdala is indispensable for emotional conditioning and for coupling of exteroceptive sensory information with interoceptive information concerning emotions and affect (Bechara et al. 1995).

It seems reasonable to assume that structural and functional deficits in these brain regions are associated with the failure of many schizophrenia patients in the higher integrative and associative brain functions, leading to distorted interpretations of the external reality (Stevens 1973; Torrey and Peterson 1974; Bogerts 1989, 1991; Bogerts et al. 1987).

In addition to bidirectional connections with the association cortex, the amygdala and hippocampus project by several fiber bundles to phylogenetically old brain parts (septum, hypothalamus, midbrain, pons, medulla) that are thought to play a crucial role in the neuronal generation of basic drives and emotions (Hess 1949) and were called by McLean (1952) the "reptilian brain." The amygdala projects via stria terminalis and ventral amygdalofugal fibers and the medial forebrain bundle to the hypothalamus, septum, midbrain, and medulla; the hippocampus influences the old brain regions indirectly via amygdala and accumbens, fornix, mamillary body, and mamillotegmental tract (Nieuwenhuys et al. 1988).

Taken together, the arrangement for projections from and to the limbic key structures of the medial temporal lobe suggests that temporolimbic structures are functionally and anatomically interposed between the neocortical association areas and the "reptilian brain." Since there are no direct connections between the neocortex and the hypothalamus (Palkovits and Zaborsky 1979; Swanson 1983), integration and coordination of the higher and phylogentically new cognitive activities with the primitive reptilianlike basic drives and emotions require the intact neuronal mediation of the temporolimbic key structures. These are the amygdala complex and the hippocampus with its gate, the entorhinal cortex, and to some extent the orbital cortex.

Thus, in addition to disturbed sensory-information processing, limbic pathology can theoretically be linked to the dyscontrol syndrome of basic drives and emotions

as frequently seen in schizophrenia cases (Bogerts 1989, 1991).

It is characteristic for most paranoid schizophrenia patients to feel that everything they observe is centered around them and directed against them. According to Conrad (1958), these patients are unable to perform the "Kopernicanian turn." This means they are unable to interpret events around them in a broader context; they cannot recognize that they are not the threatened center of the world, but only a piece of a larger social system that turns around other centers. Hemsley (1987) presented a neuropsychological explanation for this phenomenon. He postulated, as basic to the schizophrenic condition, a weakening of the influences of stored memories on current perception. Gray and McNaughton (1983) and Millner (1992) proposed the hippocampal-septum system as the crucial site in the brain where the comparison of past and present is made; it is the interplay between hippocampus and associated neocortex that analyzes and recognizes environmental contexts. These considerations, too, lead to seeing the hippocampal formation and entorhinal cortex as important sites of dysfunction in schizophrenia.

Feer (1994) has presented a modification of the limbic-system theory of schizophrenia discussed in previous articles (Bogerts 1985, 1989, 1991, 1993). Feer suggests that the amygdala, with its connections to the orbital parts of the prefrontal cortex and the lower brainstem, is involved in phylogenetically older functions than is the hippocampus, with its recurrent projections to the dorsolateral prefrontal cortex. He points out that the amygdala performs basic emotional assessment, as well as positive and negative reinforcement of incoming environmental stimuli. Feer adds that destruction of the amygdala leads to passive behavior and lack of normal explorative activities, while stimulation of this nucleus causes increased reactions of arousal and startle, vegetative symptoms, and anxious behavior (Halgren 1992; Rolls 1992).

Feer also speculates that the phylogenetically younger hippocampal-prefrontal system is hierarchically superior to the older amygdala system and suppresses the primitive amygdala reactions. Therefore, hippocampal pathology leads to a dysinhibition of the amygdala circuits; this in turn produces the behavior that in patients will be diagnosed as psychotic. However, physiological evidence that hippocampal output suppresses activities of the amygdala circuits is still missing.

Findings Supporting the Limbic System Theory of Schizophrenia

Schizophrenialike Symptoms in Organic Brain Diseases. Long before the first postmortem and mag-

netic resonance imaging (MRI) studies in the limbic structures of schizophrenic cases, researchers knew that organic lesions in limbic and paralimbic structures of the temporal and frontal lobe are much more frequently associated with schizophrenialike symptoms than are lesions of the parietal and occipital lobes, basal ganglia, and brainstem (Mulder and Daley 1952; Davison and Bagley 1969; Torrey and Peterson 1974). Viral infections with high affinity to the medial temporal lobe (e.g., herpes simplex, encephalitis, rabies) often produce, in their early stages, severe emotional symptoms of fear, aggression, anxiety, irritability, periods of apathy or restlessness, overattention to external stimuli, distractibility, inappropriate sexual behavior, and even paranoid symptoms and hallucinations (Greenwood et al. 1983). The same symptoms can be caused by medial temporal lobe tumors, infarctions, traumas (Hillbom 1951; Mulder and Daley 1952; Malamud 1967; Davison and Bagley 1969), and temporal lobe epilepsy, especially if the lesion is on the left side and originated in the fetus or perinatally (Flor-Henry 1969; Roberts et al. 1990). At least in the initial stages, such organic brain diseases are frequently misdiagnosed as schizophrenia.

Pathoanatomical Findings in Limbic Structures of Schizophrenia Patients. It is well established that at least in a substantial subgroup of patients, there are subtle structural changes in limbic structures of the medial temporal lobe. In 1982, I started to assess brains of schizophrenia patients and normal control subjects of the Vogt collection morphometrically, performing volume measurements of several basal ganglia and limbic structures. The major temporolimbic structures—hippocampal formation, parahippocampal gyrus, and amygdala, as well as the internal segment of the pallidum—proved to be significantly smaller in the patients (Bogerts 1984; Bogerts et al. 1985). Subsequent analysis of volumes and cell counts in hippocampus and pallidum showed that cell numbers in the pallidum were reduced in the catatonic patients, while paranoid patients had lower neuron numbers in the hippocampus (Bogerts et al. 1986; Stevens 1986). None of the patients were treated with neuroleptic drugs.

Since my initial report, some 30 other quantitative or qualitative anatomical postmortem studies and about 20 MRI studies on the limbic structures of schizophrenia patients have been published. There are several comprehensive reviews of the findings on limbic structures and other brain regions (Bogerts and Lieberman 1993; Shapiro 1993). The majority of postmortem and MRI studies found subtle structural changes in at least one of the investigated limbic regions.

More recently, Arnold et al. (1995) described smaller neuron size in hippocampal subfields that mediate cortical

hippocampal interplay. However, several studies have yielded negative results as well. Consistent with earlier results, three more recent MRI studies found reduced volumes of hippocampus (Bogerts et al. 1993*b*; Marsh et al. 1994) and parahippocampal gyrus (Kawasaki et al. 1993). Two others could not confirm this (Colombo et al. 1993; Zipurski et al. 1994).

A crucial aspect of mesiotemporal structure morphometry is that the reported changes are subtle, the structures are small, and they have an irregular shape. Therefore, well-defined delineation criteria, consistent anatomical landmarks defining the starting and ending points of measurements, and thin MRI slices are necessary to detect the changes. Moreover, in a disease with a biological basis believed to be heterogeneous (Carpenter et al. 1993), sampling effects in addition to measurement problems may yield negative results. The prediction, therefore, is justified that not all future anatomical studies of temporolimbic studies in schizophrenia will report significant differences to controls. A minority of research articles will fail to provide results reaching the level of significance, especially if they include patients in whom other than positive symptoms prevail.

Anatomical Findings in Cortical Structures Closely Related to the Mesiotemporal System. The first morphometric studies on brain tissue components in schizophrenia focused on the hippocampus, parahippocampal gyrus, amygdala, and temporal horn. Recently, several authors have presented evidence that in addition to temporolimbic alterations, there are more widespread volume reductions of cortical association areas that project to—or receive projections from—mesiotemporal structures.

Schlaepfer et al. (1994) showed that the heteromodal association cortex (dorsolateral prefrontal cortex, inferior parietal lobule superior temporal gyrus), but not the occipital and sensorimotor areas, is significantly reduced in schizophrenia patients. No such differences were seen between bipolar patients and controls. This finding supports the notion that higher integrative functions of the supramodal association cortex closely linked to the limbic system are impaired in schizophrenia. Similarly, frontal and perisylvian, (but not occipitoparietal) cerebrospinal fluid volume enlargement was found in computerized tomography scan studies by Bogerts et al. (1987) and by Raz (1993); schizophrenia patients had significantly more perisylvian atrophy than patients with mood disorders. Thus, among the so-called endogenous psychoses, tissue loss in perisylvian structures appeared to be specific for schizophrenia. Diffuse tissue reduction by 4 to 5 percent in frontal and temporal cortical gray matter and corresponding sulcal enlargement also was reported by Harvey

et al. (1993); in that study, the most common significant finding in male and female patients was bilateral sylvian fissure enlargement. At the neurohistological level, reduction of neuropil associated with increased neuronal densities was demonstrated in the dorsolateral prefrontal cortex, a structure intensively connected with the medial temporal lobe (Selemon et al. 1995).

Indirect evidence of a predominant temporal lobe involvement was provided by an MRI study of the corpus callosum (Woodruff et al. 1993). A significant area difference between patients and controls was seen in the mid-corpus callosum, which communicates between the temporal lobes.

Thus, several investigations indicate that in addition to temporolimbic pathology, more widespread cortical regions are affected in schizophrenia. Within the cortex, heteromodal association areas in the frontal and temporal lobe, including perisylvian regions, seem to be more affected than occipital areas. The reported reductions in cortical volume and whole-brain volume do not exceed 5 to 6 percent, while in some studies hippocampal volume reduction in chronic-treatment, refractory patients reached 10 to 20 percent (Bogerts et al. 1993*b*; Marsh et al. 1994).

Postmortem Neurochemical Findings in Limbic Structures. A large number of postmortem pharmacological studies in limbic and temporal lobe structures have been published (for review, see Reynolds 1989; Seeman and Niznik 1990; Lieberman and Koreen 1993; Shapiro 1993). While studies in dopamine receptor subtypes used mainly tissue obtained from the striatum (Seeman and Niznik 1990), a multitude of neurotransmitter receptor binding sites and transmitter uptake sites were studied postmortem in the temporal cortex and mesiotemporal structures of schizophrenia cases.

In a comprehensive review of postmortem studies in schizophrenia, Shapiro (1993) concluded that very little, if any, of this biochemical work is directly comparable—either in terms of the brain region examined or the method used to characterize the binding site in question. Thus, there remains a largely open question as to what extent postmortem neuropharmacological data are affected by either the length of the medication-free interval before death, the length of the agonal period, or the method used to prepare the tissue.

Nearly all brain regions investigated by postmortem neurochemistry show some abnormalities in neurotransmitter receptors and uptake sites. Temporolimbic structures do not stand out as being specifically affected. However, some findings supporting the temporolimbic theory of schizophrenia should be mentioned here:

1. Reynolds (1989) reported increased dopamine concentrations in the left amygdala. The same group (Reynolds et al. 1990, as well as Simpson et al. 1989), later found deficits in gamma-aminobutyric acid (GABA) uptake sites in the left more than the right hippocampus, but not in the amygdala.

2. Farmery et al. (1985) reported reduced cholecystokinin binding in the hippocampus and frontal cortex of schizophrenia subjects.

3. Kerwin et al. (1988) and Deakin et al. (1989) found glutamatergic dysfunction in the left temporolimbic regions, while Kerwin et al. (1992) found reduced cholecystokinin-B binding in the parahippocampal gyrus, the subiculum, and a hippocampal cornu ammonis 1 subfield segment.

4. Joyce et al. (1993) reported increased numbers of serotonin receptors and uptake sites in the limbic regions of the striatum, limbic cortex, and hippocampus.

5. In a study linking limbic and prefrontal pathology as well as phencyclidine psychosis to schizophrenia, Tsai et al. (1995) demonstrated that changes in N-acetyl aspartylglutamate (NAAG) and its cleaving enzyme N-acetyl-α-linked acidic dipeptidase (both substances being markers for glutamatergic neurons) were selectively restricted primarily to the prefrontal cortex and hippocampus.

In general, biochemical data are more vulnerable to pre- and postmortem artifacts (medication, agonal state, postmortem delay) than to morphological parameters such as volumes, cell numbers, and cytoarchitectural features. A further advantage of neuroanatomical data is that the macroscopic area and volume measurements obtained from postmortem tissue can be validated by in vivo MRI measurements. Nevertheless, the above-mentioned biochemical studies also point to the limbic system as an important site of dysfunction in schizophrenia.

Clinical Correlates of Temporolimbic Pathomorphology. If structural and functional abnormalities of the temporolimbic system can cause at least some symptoms of the broad spectrum of schizophrenia, then the degree of pathomorphology should correlate with the intensity of these clinical symptoms. A remarkable study addressing this question was performed by Degreef et al. (1992a); they measured the volumes of the frontal, occipital, central, and temporal components of the lateral ventricles in first-episode schizophrenia cases, as well as third and fourth ventricles. The temporal horn was subdivided in an anterior (amygdala) portion and a posterior (hippocampal) portion.

More left than right enlargement was observed in all components of the lateral ventricles. Delusions, hallucinations, and bizarre behavior correlated selectively with enlargement of the posterior portion of the left temporal horn, reflecting structural abnormalities in the left hippocampal region. In contrast, the left anterior temporal horn, reflecting amygdala and anterior hippocampal abnormality, correlated significantly only with anhedonia. All other portions of the ventricular system showed few or no tendencies toward correlations. This finding is especially important with regard to Feer's (1994) above-mentioned theory linking hippocampal but not amygdala hypofunction to positive schizophrenic symptoms.

Bilateral temporolimbic pathology may predispose one to a chronic course of psychotic symptoms. Bogerts et al. (1993b) found an inverse correlation between total amygdala plus hippocampal volume and positive but not negative symptoms in both hemispheres of chronic schizophrenia patients.

In addition to mesiotemporal lobe pathology, two groups reported decreased volume of the left superior temporal gyrus, which is not a part of the limbic system but belongs to the auditory association cortex (Barta et al. 1990; Shenton et al. 1992). Volume reduction of this gyrus was highly correlated with thought disorder and auditory hallucinations. However, the finding of superior temporal gyrus volume was not replicated by Zipurski et al. (1994).

Neuropsychological assessments of schizophrenia cases reported associations between hippocampal (Goldberg et al. 1994) or whole temporal-lobe volume (Nestor et al. 1993) and impaired verbal memory, abstraction, and categorization—as well as executive and motor functions (Bilder et al. 1995). Pathomorphological changes in the temporolimbic system seem to correlate with other biological variables. Also found are associations between mesiotemporal structures and reduced visual and auditory N200 amplitude, as well as between the right hippocampus and visual P300 (O'Donnell et al. 1993; Egan et al. 1994).

We assume that clinical correlates of the various pathomorphological findings in schizophrenia probably will remain a subject of controversy. A lack of homogeneity of patient populations and anatomical findings, plus the instability of psychotic symptoms over time, make it difficult to find consistent clinical-anatomical correlations. Moreover, in addition to brain morphology, biochemical, psychosocial, and other factors may determine the clinical picture.

Functional Studies of Temporolimbic Regions in Schizophrenia Cases. While structural data obtained by necropsy or MRI tend to indicate temporal lobe abnormalities, functional imaging studies have emphasized frontal lobe hypometabolism that seems to be characteristic for

chronic patients with predominantly negative symptoms (Ingvar and Franzen 1974). More recent studies have related psychopathological subtypes of the disease to different abnormalities of brain perfusion patterns.

Some functional imaging studies, too, indicate that positive symptoms of schizophrenia (delusions, hallucinations, paranoid ideas) are associated with temporolimbic dysfunctions. Using the regional cerebral blood flow (rCBF) method with the [15]oxygen-inhalation technique, three symptom clusters have been reported to be associated with a distinct pattern of rCBF abnormalities: Delusions and hallucinations ("reality distortion") were associated with increased rCBF in the left mesiotemporal lobe structures. Thought disorder and inappropriate affect ("disorganization") were associated with increased rCBF in the right anterior cingulate cortex, left superior temporal gyrus, and dorsomedial thalamus, whereas negative symptoms ("psychomotor poverty") were related to reduced blood flow in the left prefrontal and parietal cortex (Liddle et al. 1992).

A subsequent statistical analysis by the same group (Friston et al. 1992) found the most remarkable correlation between the sum of the three subsyndrome scores and left parahippocampal gyrus blood flow. Disinhibition of left medial temporal lobe activity mediated by frontolimbic connections was regarded as a possible explanation for the findings.

Perfusion abnormalities in the hippocampus and anterior cingulate cortex in actively psychotic patients were also shown by a study using positron emission tomography, while patients with deficit symptoms also showed hypometabolism in frontal parietal and thalamic areas (Tamminga et al. 1992). Using single photon emission tomography in chronic schizophrenia patients, Kawasaki et al. (1992) found increased relative blood flow in the left hippocampal region and an inverse correlation between prefrontal cortical blood flow and negative symptoms.

Associations Between Hippocampal Pathology and Prefrontal Dysfunction. In addition to limbic dysfunction, there is overwhelming evidence for prefrontal cortical involvement in the pathophysiology of schizophrenia (Weinberger 1987; Weinberger et al. 1992; Goldman-Rakic 1994). Since there are close functional connections between the hippocampal formation and the prefrontal cortex (Goldman-Rakic et al. 1984), it is not surprising that prefrontal lobe dysfunction and hippocampal pathology can occur in the same patients.

In the monozygotic twin study of Weinberger et al. (1992), in virtually all pairs the affected twin had reduced hippocampal volume and lower prefrontal rCBF, compared with the unaffected twin. Moreover, there was a

highly significant correlation between hippocampal volume reduction and prefrontal dysfunction, suggesting that normal prefrontal activity depends upon input from an undisturbed hippocampal formation. This view is supported by a comprehensive neuropsychological study in first-episode schizophrenia patients (Bilder et al. 1995); it demonstrated a significant correlation between anterior hippocampal volume and lower scores on measures of executive and motor functions—indicating impaired limbic control of frontal-lobe activities.

Direct support of a close association between mesiotemporal and prefrontal pathology was provided by an MRI scan study by Breier et al. (1992): Reduction of right prefrontal white-matter volume was significantly related to reduced right amygdala/hippocampal volume. The data suggested the hypothesis of altered connections between the limbic system and prefrontal cortex. In a comprehensive review, Weinberger and Lipska (1995) proposed that schizophrenia can best be explained by a disconnection syndrome between temporolimbic and prefrontal cortices. These authors emphasized that metachromatic leukodystrophy, a disease that affects diffuse fiber connections between frontal and temporal lobes, appeared to be the best neurological model of schizophrenia.

Neurodegeneration or Early Acquired Dysplasia?

Kraepelin (1899) defined dementia praecox as a chronic progressive disease with a poor outcome. He therefore assumed a progressive neuropathological process underlying the disease. Several lines of evidence, however, argue against this assumption. They demonstrate that, in the long-term course of the disease, most patients do not show a progressive pyschopathology, especially positive symptoms do not worsen over time, and there is no evidence for progressive limbic brain pathology. Instead, static, nonprogressive, and subtle limbic-system abnormalities could be shown, probably resulting from disturbed prenatal or perinatal brain development. Anatomical findings in favor of the subtle abnormality of prenatal brain development are (1) cytoarchitectural abnormalities in the limbic, frontal, and temporal cortical areas; (2) lack of gliosis in affected brain regions, such as limbic structures and thalamus; and (3) lack of progressive tissue loss in postmortem and MRI followup studies.

Abnormalities in Prenatal Brain Development. Substantial disability may result not only from developmental deformities of the brain that are grossly evident at birth, but also from subtle disorders of development in

functional key structures of the brain. These lesser distur- bances may be ascertained only by their functional conse- quences, such as learning problems, language disorders, autism, and recurrent seizures. It is probable that these milder disorders reflect, in most instances, disturbances of the later stages of brain development—that is, the processes of growth and differentiation of tissue compo- nents (Caviness 1989). It is now clear that at least a sub- stantial subgroup of the schizophrenias belongs to this group of diseases. The following findings of abnormal limbic and cortical architecture are strong indicators of a disorder of the third stage of prenatal brain develop- ment—the settling of neurons in their final neocortical or archicortical positions.

Ernst Wagner's brain showed a subtle but unequivocal focal developmental anomaly (cortical invagination) in the left posterior entorhinal cortex (Bogerts 1997). In a signifi- cant percentage of patients suffering from schizophrenia, subtle cytoarchitectural anomalies were described in the hippocampal formation (McLardy 1974; Kovelman and Scheibel 1984; Conrad et al. 1991); in the frontal and tem- poral cortex and the cingulate gyrus (Benes et al. 1986; Benes and Bird 1987; Akbarian et al. 1993*a*, 1993*b*); and in the entorhinal cortex (Jakob and Beckmann 1986; Falkai and Bogerts 1989; Arnold et al. 1991).

Degreef et al. (1992*b*) reported developmental abnormalities in the septum, which is a limbic structure closely connected with the hippocampus. Clearly, the cytoarchitectural findings need replication by other groups. Still, it is remarkable that studies of different brain regions by different laboratories came to the con- clusion that there are cytoarchitectural deviations that can be explained only by a disorder of the later stages of pre- natal brain development.

Lack of Gliosis in Limbic Structures. Increase in glial- cell densities and glial-cell fibers indicate acute or chronic brain tissue destruction acquired perinatally or after birth, whereas early developmental lesions are not followed by gliosis. While earlier qualitative studies and one recent quantitative study described gliotic reactions in brainstem and periventricular regions (Fisman 1975; Stevens 1982; Bogerts et al. 1993*a*), none of the quantitative studies of glial-cell densities could show an increase in glial elements in the affected mesiotemporal structures. On the contrary, in the hippocampus, parahippocampal gyrus, cingulate gyrus, and thalamus, both neuronal and glial-cell elements were reduced. Neuron-glia ratios were unchanged (Falkai and Bogerts 1986; Benes and Bird 1987; Falkai et al. 1988; Pakkenberg 1990; Casanova 1991; Casanova et al. 1991). This indicates that neurons and glia cells are affected by a disorder of brain development.

No Correlation to Disease Duration. Similar to ven- tricular enlargement (Raz and Raz 1990), limbic-system pathology does not seem to be progressive in schizophre- nia patients. Neither postmortem (Bogerts et al. 1985, 1990) nor MRI scan studies (Bogerts et al. 1993*b*; Marsh et al. 1994) show a positive correlation between hip- pocampal volume reduction and disease duration, again supporting the view that the structural changes in the lim- bic system are acquired before the onset of the psychotic symptoms and then remain static.

Is the Left Temporal Lobe More Affected Than the Right?

Since language functions are localized in the left hemi- sphere of most individuals, it is reasonable to assume that auditory hallucinations (e.g., imperative and commenting voices and dialogs) are caused by an overactivity (possi- bly a dysinhibition) of the sensory-language centers in the left temporal lobe. Indeed, more left than right temporal- lobe pathology has been demonstrated for the superior temporal gyrus (Barta et al. 1990; Shenton et al. 1992), the hippocampal formation (Bogerts et al. 1990), the parahippocampal gyrus, and the temporal horn (Crow et al. 1989; Degreef et al. 1992*a*, 1992*b*). Left, but not right, temporal horn enlargement and superior temporal gyrus reduction correlated with positive schizophrenic symp- toms (Barta et al. 1990; Degreef et al. 1992*a*, 1992*b*; Shenton et al. 1992).

Abnormal brain perfusion in left but not right mesio- temporal structures was found in schizophrenia patients (Kawasaki et al. 1992), especially those with "reality dis- tortion" (Liddle et al. 1992). Friston et al. (1992) showed that rCBF in all subsyndromes of schizophrenia was most abnormal in the left parahippocampal gyrus. At the neu- ropharmacological level, limbic abnormalities in dopaminergic, GABAergic, and glutamatergic mecha- nisms mainly have been found in the left hemisphere (Kerwin et al. 1988, 1992; Deakin et al. 1989; Reynolds et al. 1990).

Predictions, Questions, Future Tasks

The extent of pathomorphological changes seen in the temporolimbic structures of schizophrenia patients is small and does not begin to reach the degree of tissue loss in the well-known degenerative brain diseases. Moreover, there is a considerable overlap of the morphometric data from schizophrenia cases with the normal control range. The diversity of the morphological changes can be seen even by mere qualitative inspection of MRI scans

(Lieberman et al. 1992). In terms of the diversity of clinical symptoms and the instability of psychotic symptoms over time (Carpenter et al. 1993; Bogerts 1993)—and given the subtlety of the anatomical changes—it is not surprising that not all past studies found differences to controls. Therefore it is justified to predict that in the future, most studies of temporal lobe morphology and related clinical anatomical correlations will yield positive results. A minority of authors will continue to demonstrate lack of temporolimbic pathology in schizophrenia.

The mesiotemporal structures, hippocampus, amygdala, and parahippocampal gyrus consist of a multitude of histological and functional subunits that may be affected differently in the various psychopathological pictures of positive schizophrenia syndromes. Detecting these presumed limbic subtypes of schizophrenia will be a domain of future postmortem neurohistology; the resolution of modern brain-imaging methods is not high enough to subdivide small limbic-tissue components.

The small amount of tissue reduction in the hippocampus and parahippocampus of schizophrenia cases (10% to 30%, compared with controls) suggests that some cellular subfractions within these structures (e.g., interneurons, collateral fibers, special receptor types, other yet-unknown components) might be lost. Further analysis will detect such tissue components that could be disease specific.

There are known diseases of the limbic system other than schizophrenia. Temporal lobe epilepsy, Wernicke-Korsakow syndrome, and the temporal forms of Pick's and Alzheimer's disease also affect key limbic areas in the brain. These diseases, however, differ from paranoid schizophrenia in type, severity, and regional distribution of the histological lesions. Focal loss of neurons and glial scars occur in temporal lobe epilepsy (Roberts et al. 1990). In Wernicke-Korsakow syndrome, limbic diencephalic areas surrounding the third ventricle (but not the temporal lobe) are the focus of pathology. In Alzheimer's and Pick's diseases, the frequently occurring complete degeneration of the hippocampus/parahippocampus is regularly associated with extensive damage in other cortical and subcortical areas.

The nonschizophrenic disorders of the limbic system are associated with gliosis, indicating progressive brain diseases acquired later in life, while most authors agree that schizophrenia patients suffer from an early acquired developmental disorder. There are reports that some types of temporal epilepsy are also caused by subtle developmental abnormalities in the medial temporal lobe. However, these forms of epilepsy show many symptoms in common with schizophrenia (Roberts et al. 1990).

The question that remains is why the temporolimbic subtype of schizophrenia is not associated with the memory loss typical for organic lesions of these areas (Jernigan and Cermak 1994). A possible answer is that classic amnestic syndromes require massive tissue destruction, as seen after surgical lesions, tumors, injuries, or infections or in Alzheimer's disease. In Korsakow's syndrome, other memory-relevant tissue components in the thalamus and hypothalamus are also affected.

In schizophrenia, we observe subtle developmental structural deviations that lead to dysfunction (or predispose to a breakdown of normal function) under the influence of additional stressors, but not to a complete loss of function. Research has shown that circumscribed developmental lesions in the hippocampus of experimental adult animals produce symptoms that resemble more prefrontal dysfunctions than do memory deficits occurring after lesions in adults (Weinberger and Lipska 1995).

While schizophrenia patients apparently do not have typical amnestic syndromes, memory impairment has been found to be disproportionate to the overall level of intellectual and other neuropsychological impairment (McKenna et al. 1990), especially semantic memory was reported to be impaired (McKay et al. 1996). Schizophrenia patients also have another type of memory problem: They are unable to perform the "Kopernicianian turn" because, according to the above-mentioned theory of Gray (1982) and Hemsley (1987), there is a disturbance of the interplay between hippocampus and the associated neocortex that analyzes and recognizes environmental contexts by comparing past and present experiences.

I believe that the various types of structural abnormalities in the brains of schizophrenia subjects are vulnerability or trait markers. These predispose the brain to decompensate under the influence of additional factors related to the vulnerable period between puberty and old age, and to stress. Those factors may include late myelination in the frontal or limbic cortex (Weinberger 1987; Benes 1989; Benes et al. 1994); steroid hormones (Bogerts 1989); abnormal synaptic sprouting (Stevens 1992); or psychosocial stressors (Zubin and Spring 1977; Bebbington et al. 1995).

To make substantial advances in the therapy of schizophrenia, we must learn more about the interaction between vulnerable limbic structures and the age- and stress-related hormonal and transmitter components that lead to either decompensation or recovery of a patient's brain. Interestingly, the stress hormone, cortisol, has high receptor densities in the hippocampus and causes, via genomic effects, a long-lasting inhibition of hippocampal neurons (Vidal et al. 1986; McEwen et al. 1992). Other steroid hormones, neuropeptides, and transmitters related to age and stress could have similar effects. Therefore,

stress and pathomorphology could have a final common pathway in paranoid schizophrenia. The search for new strategies to prevent the disastrous neurobiological effects of stress on a vulnerable limbic system is one of the most important tasks for future schizophrenia research.

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