Eur Arch Psychiatry Clin Neurosci (1995) 245:224–230

Michael B. Knable · Daniel R. Weinberger

Are mental diseases brain diseases? The contribution of neuropathology to understanding of schizophrenic psychoses

Received: 10 October 1993 / Accepted: 6 February 1995

Abstract Nearly a century after the seminal contributions of Emil Kraepelin, the search for neuropathologic correlates of schizophrenic psychoses continues. A multitude of neuroanatomic and neurochemical findings has emerged in recent years, but many of these findings are not replicated or are difficult to interpret in light of methodologic problems. In this review replicated neuropathologic and neuroimaging studies are discussed. The hypothesis that emerges from these studies is that schizophrenia is a developmental abnormality affecting the connectivity of the prefrontal and medial temporal cortices.

Key words Schizophrenia · Psychosis · Neuropathology · Neuroimaging

Introduction

Emil Kraepelin's writings were among the most substantial arguments of his time for the consideration of psychotic disorders as brain diseases. In *Dementia Praecox* (1919) Kraepelin reasoned from careful, longitudinal, clinical observations that schizophrenic symptoms resulted from pathology of the nervous system, particularly the frontal and temporal lobes of the brain. Kraepelin's approach to behavioral neuropathology was characteristic of his era of cerebral localizationists. His thinking had been strongly influenced by neurologists such as Broca (1863), Wernicke (1874), and Lichtheim (1885), who had correlated the presence of focal cerebral lesions with deficits in language function. It was logical then that Kraepelin's neuropathologic investigations searched for the presence of a focal, if not a pathognomonic, brain lesion.

Kraepelin's thinking was also in accord with contemporaries, such as Alzheimer, who had recently attributed senile mental changes to degenerative neuropathologic findings. Kraepelin's clinical concept of schizophrenia as an early-onset and often progressive dementia was logically attributable to a degenerative condition of the brain, and indeed, degenerative neuronal pathology had been reported in some of the earliest neuropathologic observations about schizophrenia.

Kraepelin reviewed the neuropathologic literature that preceded him in his textbook and offered neuropathologic studies of his own. His brain specimens from patients with dementia praecox were found to have swollen neuronal nuclei, shrunken neuronal cell bodies, neuronal lipoid deposits, neuronal loss, and hyperplasia of glial elements in multiple areas of cerebral cortex. While other authors of his time reported similar findings, the neuropathologic literature of the 19th and early 20th century is most notable for its inconsistencies and general lack of adequate controls for the artifacts of normal aging, agonal state, postmortem interval, and tissue processing (For review of the older neuropathologic literature see Weinberger et al. 1983).

While Kraepelin's notion of schizophrenia as a brain disease prevails presently, modern research has moved away from his assumption that a localized or specific degenerative brain lesion would be discovered. Increasingly, schizophrenia is seen as a developmental abnormality of cerebral cortex that is associated with aberrant interactions of functionally related cortical areas. Interestingly, Kraeplin also believed that some cases of schizophrenia were the result of congenital brain damage, but he regarded these cases as exceptions. It is increasingly believed presently that the cerebral dysfunction in most cases of schizophrenia is congenitally predetermined. Opportunities to test these propositions have improved with the development of new neuroimaging and neuropathologic techniques, which are reviewed herein.

Dr. M. B. Knable (✉) · R. Weinberger
National Institute of Mental Health, National Institutes of Health, Intramural Research Program, Clinical Brain Disorders Branch, 2700 Martin Luther King Jr. Ave., S.E., Washington, D.C. 20032, USA

Macroscopic brain abnormalities in schizophrenia

Enlarged cerebral ventricles and dilatation of cortical sulci in schizophrenia, observations from neuropathologic

literature that predated even Kraepelin, have been supported by a large number of recent studies. Ewald Hecker, who influenced Kraepelin with his concept of hebephrenia, described enlarged cerebral ventricles in postmortem specimens from psychotic patients in 1871. A number of pneumoencephalographic (PEG) studies followed, which not only described enlargement of the cerebral ventricles (Jacobi and Winkler 1927; Asano 1967), but also found stability of ventricular size in a longitudinal study (Lemke 1935), and a correlation between ventricular size and clinical symptoms (Huber 1957; Haug 1962). Perhaps because of the inconsistencies in the neuropathologic literature and the negative PEG study of Storey (1966), the PEG literature was not widely appreciated until the advent of computed tomography (CT) and magnetic resonance imaging (MRI).

In 1976 Johnstone et al. published the first controlled CT study of cerebral ventricular enlargement in chronic schizophrenia, which confirmed the results of earlier PEG work. The majority of subsequent CT studies (for review see Zigun and Weinberger 1992) have replicated this finding, despite the methodologic problems of CT measurements for between-group comparisons (Cleghorn et al. 1991). No consistent relationship has been found between ventricular size and age, duration of neuroleptic exposure, electroconvulsive therapy, or duration of illness. However, enlarged ventricles do correlate in some studies with poor premorbid social and educational adjustment, cognitive impairment, more negative symptoms, diminished response to neuroleptic treatment, and a greater frequency of drug-induced extrapyramidal movement disorders. Further evidence against ventriculomegaly as an epiphenomenon is the observation of ventriculomegaly in "first-break" patients with schizophrenia (Nyback et al. 1982; Schulz et al. 1983; Weinberger et al. 1982; Iacono et al. 1988) and in affected members of discordant sibships including monozygotic twins (Weinberger et al. 1981; Revely et al. 1982; DeLisi et al. 1986; Suddath et al. 1990). Ventricular enlargement also appears to be a stable finding in follow-up CT studies (Illowsky et al. 1988; Sponheim et al. 1991), implying that the underlying pathology is not progressive or degenerative. A number of MRI studies have replicated the PEG and CT studies (Kelsoe et al. 1988; Suddath et al. 1990; Gur et al. 1991; Young et al. 1991; DeLisi et al. 1991; Degreef et al. 1992; Zipursky et al. 1992).

Postmortem studies in which modern diagnostic criteria, adequate control groups, and quantitative measurement techniques have been applied have also confirmed the CT and MRI scan literature. Brown et al. (1986) compared schizophrenics to affective-disorder controls and found that schizophrenic brain samples were 6% lighter and had lateral ventriculomegaly that was prominent in the temporal horns. Pakkenberg (1987) found her schizophrenic brain sample to have reduced volume of the total brain, the hemispheres, and the gray matter of the cerebral cortex. Volumes of the lateral ventricles were larger in the schizophrenic group particularly if patients had suffered from prominent deficit symptoms. Pakkenberg's study is also of interest in that once again ventricular size did not correlate with length of illness; it did correlate, however, with deficit symptoms that were present at illness onset, but not those present near death. The latter finding further suggests that the cause of ventriculomegaly is present at least at the onset of illness and is not progressive.

Schizophrenia and the medial temporal lobe

If patients with schizophrenia are found to have enlarged cerebral ventricles and reductions in the volume of cerebral cortex, one may next logically wonder if these findings are secondary to a generalized process affecting the entire cerebral gray matter or could be explained by reduced volume of one or several brain areas. While the weight of the neuropathologic evidence favors a nonfocal, generalized process, there is considerably more data about the involvement of certain areas. Medial-temporal-lobe structures have particularly been the subject of active study in recent years, because many patients with neurologic lesions of the medial temporal lobe have psychotic symptoms (Davison and Bagley 1969) and because many patients with schizophrenia manifest memory deficits on neuropsychologic testing (Goldberg et al. 1991). Kraepelin himself argued that temporal lobes were a likely site of disease in schizophrenia.

Scheibel and Kovelman (1981) studied brain tissue of eight chronically hospitalized schizophrenic subjects with a qualitative Golgi technique and found profound disturbances in orientation of hippocampal pyramidal cells and their dendritic arborizations. In a quantitative study using Nissl and Golgi techniques these authors (Kovelman and Scheibel 1984) found pyramidal cell disarray in the left hippocampi of 10 chronic schizophrenics. Pyramidal neurons from the schizophrenic sample were significantly more deviated from an axis drawn perpendicularly to the ventricular surface. This finding was most pronounced in the anterior and middle hippocampus at the cornu ammonis (CA)1-prosubiculum and the CA1/CA2 interfaces. Pyramidal cell disarray was observed, despite normal neuronal cell density. Abnormalities in pyramidal cell orientation, in the absence of cell loss or gliosis, were interpreted by the authors to represent a disruption of neuronal migration or segreation during development of the hippocampal cortex. A subsequent report of identical findings in the right hemisphere led the authors to conclude that hippocampal cell disarray was a bilateral phenomenon (Conrad et al. 1991). Unfortunately, three groups have been unable to replicate these results. Altshuler et al. (1987) and Christison et al. (1989) were unable to identify pyramidal cell disarray in samples from the Yakovlev collection. Benes et al. (1991) were also unable to identify pyramidal cell disarray in a subjective assessment of samples in their collection. The lack of independent replication of hippocampal pyramidal cell disarray leaves the validity of this finding in doubt.

Jakob and Beckmann (1986) have described another abnormality in the medial temporal lobe of schizophrenic

patients that is thought to represent a defect in cortical development. They examined the entorhinal and insular cortices in 64 cases of schizophrenia and in 10 nonschizophrenic controls with Nissl staining. Approximately one-third of their cases had definite cytoarchitectural abnormalities, one-third had equivocal findings, and one-third had no abnormalities. Specifically, the abnormalities consisted of heterotopic groups of neurons that extended from the pre-α to the pre-β cortical layer, pre-α neurons that lied in a laminar rather than in a glomerular pattern of organization, and a reduction in cell numbers in the ventral insular area. These findings were especially prominent in rostral, medial, and central areas of the entorhinal cortex, were present in both hemispheres, but were more conspicuous on the left, and were more likely present in cases with the hebephrenic subtype. The temporal neocortex did not exhibit histoopathologic abnormalities. The investigators in this study were not blinded to diagnosis, their patients may have been somewhat atypical (e.g., the mean age of illness onset was 36 years), and their control group may not have been large enough to define the normal range of variability in entorhinal cortical anatomy. Nevertheless, Jakob and Beckmann's results are supported by similar findings seen in six cases of schizophrenia from the Yakovlev collection (Arnold et al. 1991).

Several other groups studying postmortem tissue have reported abnormalities of the medial temporal lobe, although the results are less clearly supportive of developmental pathology. Reduced volume of the amygdala, hippocampus, parahippocampal gyrus, and entorhinal cortex have been reported (Bogerts et al. 1985; Brown et al. 1986; Colter et al. 1987; Falkai et al. 1988; Jeste and Lohr 1989; Bogerts et al. 1990a). Neuronal loss in entorhinal or hippocampal cortices (Falkai et al. 1988; Jeste and Lohr 1989; Benes et al. 1991) has also been described, but negative studies have also appeared (Heckers et al. 1991). One report of reduced size of hippocampal neurons has not been independently replicated (Benes et al. 1991). Stevens (1982) observed fibrillary gliosis in the hippocampus and in other limbic areas in schizophrenic brain samples, but this finding has not been independently replicated, and negative reports have appeared (Roberts et al. 1986). A lack of gliosis in the cortical areas that contain neuropathologic abnormalities may indicate that disruption of cortical architecture in schizophrenia is secondary to a prenatal insult.

In support of the postmortem findings in the medial temporal lobe of patients with schizophrenia, a complementary MRI literature has accumulated in recent years. A number of groups have found bilateral reductions in amygdala–hippocampal volume (Delisi et al. 1988; Suddath et al. 1989; Suddath et al. 1990; Breier et al. 1992; Marsh et al. 1993). Others have found reduced volume of these structures primarily in the left hemisphere (Barta et al. 1990; Bogerts et al. 1990b, Shenton et al. 1992). Of note are studies that have described reduced volume of the hippocampal complex in the affected members of monozygotic twin pairs discordant for schizophrenia (Suddath et al. 1990) and in first-break patients (Bogerts et al. 1990b). Young et al. (1991) found reduced volume of the parahippocampal gyrus in a group of schizophrenic patients, but DeLisi et al. (1991) were not able to replicate this findings. Reports of normal hippocampal complex volume also exist (Kelsoe et al. 1988; DeLisi et al. 1991), but these tended to employ less precise MRI methods. Interestingly, and consistent with the data concerning lack of progression of ventriculomegaly, hippocampal volume does not appear to correlate with length of illness (Suddath et al. 1991; Marsh et al. 1993).

The development of techniques for mapping in vivo physiological activity in the form of regional cerebral blood flow (rCBF) and glucose metabolism has made it possible to examine regional function brain activity in patients. Single photon emission computerized tomography (SPECT) and positron emission tomography (PET) are the principal tools for examining brain function in vivo. The advantages and disadvantages of the two techniques have been reviewed recently (Berman and Weinberger 1991). Few functional neuroimaging studies have focused on anteromedial temporal structures in schizophrenia. One would expect this area to be hypometabolic in schizophrenia, because few brain disorders, other than epileptic foci, cause hypermetabolism. Wiesel et al. (1987) found slightly reduced glucose metabolism in the right amygdala of medication-free patients, and Tamminga et al. (1988) reported a similar finding in the left amygdala and left posterior hippocampus. However, DeLisi et al. (1989) found increased glucose metabolic rates in hippocampal areas of medication-free patients that accompanied increased metabolic rates in lateral temporal cortical structures. Liddle et al. (1992) reported similar increases in left parahippocampal gyrus blood flow in a subgroup of patients. The reasons for the discrepancies are unclear and leave the temporal lobe physiologic data in a beclouded state.

Abnormalities of prefrontal cortex in schizophrenia

The neuropathologic and neuroimaging studies reviewed herein have tended to implicate parahippocampal and hippocampal cortex in schizophrenia. However, there are important problems inherent in attempting to explain schizophrenic symptoms by isolated medial temporal pathology. While patients with lesions of this area occasionally become psychotic, they typically recognize psychotic material as alien, they do not become socially withdrawn, their affect is rarely blunted, and they rarely exhibit thought disorder. Electrical stimulation of medial-temporal-lobe structures produces psychotic symptoms that are very different clinically from those seen in schizophrenia (Penfield and Rasmussen 1950). Patients with schizophrenia, although they do have memory problems, do not exhibit the amnesic syndrome typical of bilateral hippocampal area lesions.

Patients with lesions of prefrontal cortex also exhibit symptomatology that bears some resemblance to the schizophrenic syndrome. The "negative symptoms" of schizophrenia – poor motivation and drive, social with-

drawal, flat affect, impaired insight and judgment – rarely accompany damage to the temporal lobe, but are often seen in patients with frontal lobe lesions. For this reason, Kraepelin also favored the frontal lobes as a site of pathologic involvement in schizophrenia. Neuropathologic and neuroimaging studies that have reported generalized reductions in the volume of cerebral cortex, dilatation of frontal horns of lateral ventricles, and of the third ventricle in schizophrenia strongly suggest that neuronal tissue outside of the temporal lobe is also affected. If the neuropathologic process in schizophrenia occurs during cortical development, it is likely to affect at least several cortical areas simultaneously. Alternatively, a primary defect in limbic temporal cortical maturation may affect frontal and temporal neocortical development by not providing normal afferent input into these areas.

The SPECT and PET studies have not revealed consistent abnormalities in global cerebral metabolism or in laterization of brain function in schizophrenic patients. Greater consistency has emerged, however, from studies of regional physiologic activity of the prefrontal cortex. The original reports of Ingvar and Frantzen (1974a, b) of decreased frontal lobe metabolic activity ("hypofrontality") at rest have been confirmed by a number of investigators, although negative reports have also appeared (for review see Berman and Weinberger 1991).

Recently, the concept that "hypofrontality" may exist as a state-dependent phenomenon has been proposed. When measurements of regional cerebral blood flow during cognitive tasks that require intact function of prefrontal cortex are performed, schizophrenic patients are consistently hypofrontal. Weinberger et al. (1986) demonstrated a lack of activation of dorsolateral prefrontal cortex in schizophrenic patients given an automated version of the Wisconsin Card Sorting Test (WCST) during xenon-133 rCBF measurement. Similar prefrontal cortical dysfunction was not observed during performance of Raven's Progressive Matrices (RPM; Berman et al. 1988). The WCST requires that patients make decisions based on past experience and change their behavior based on error information. The RPM is an abstract reasoning task that requires as much concentration, attention, and mental effort as the WCST, but it does not require working memory in the same manner as the WCST. In studies of monozygotic twins discordant for schizophrenia, diminished activation of the dorsolateral prefrontal cortex during the WCST is invariably associated with the illness, is not present in unaffected co-twins, and is not affected by long-term neuroleptic exposure (Berman et al. 1992). Furthermore, the severity of diminished dorsolateral-prefrontal-cortex activation is correlated with diminished hippocampal volume in the affected twins, suggesting that in schizophrenia there may be a disruption of the normal communication between medial temporal and prefrontal cortical areas (Weinberger et al. 1992).

The cellular basis for the reduced prefrontal activity seen in schizophrenia is as yet unknown. Benes et al. using the Nissl technique, have described decreased neuronal density in layer VI (1986) and decreased density of small interneurons in layer II of prefrontal cortex (1991) that were not accompanied by changes in neuronal size, neuronglia ratio, or gliosis. These findings were interpreted to be the result of a developmental abnormality, because degenerative processes in the cerebral cortex typically do not affect neuronal density and are accompanied by increased glial density and neuronal shrinkage. Recently, the dorsolateral prefrontal area of five subjects with schizophrenia was found to have reduced numbers of neurons stained with nicotinamide-adenine dinucleotide phosphate-diaphorase (NADPH-d; Akbarian et al. 1993a). In white matter greater than 3 mm deep to cerebral cortex there were increased numbers of NADPH-d neurons. Similar findings were also present in the hippocampal formation and in lateral temporal neocortex (Akbarian et al. 1993b). The NADPH-d stains neurons but not glia, and substantial numbers of NADPH-d neurons are present in adult gray and white matter. These findings may be consistent with a disturbance of neuronal migration, which prevents normal development of the subplate and subsequent segregation of neurons into cortical layers. However, the relationship of any of these observations to the findings from functional neuroimaging is unclear. It should also be noted that several neurochemical abnormalities, particularly of glutamate and serotonin, have been reported in the prefrontal cortex (for review see Hyde et al. 1991).

Schizophrenia as a developmental abnormality of cerebral cortex

Because schizophrenia typically presents in the second or third decade of life and often pogresses with clinical deterioration, an adult-onset degenerative condition of the nervous system was proposed by Kraepelin and many other investigators since his time. However, recent neuropathologic studies as noted herein are not consistent with this possibility and suggest instead a developmental disorder. The stability of structural abnormalities in schizophrenia detected with in vivo neuroimaging and their presence in first-break patients implicates pathology that is nonprogressive and probably predates the appearance of diagnostic symptoms. Reductions in the volume of medial-temporal-lobe structures and in neuronal density per se, hippocampal cell disarray, abnormal lamination of the entorhinal cortex, and absent gliosis are more consistent with a developmental and arrested abnormality than with a degenerative disorder. Degenerative conditions of the brain are often associated with reactive gliosis, neuronal cell shrinkage, and markers of cellular degeneration (i.e., Lewy bodies, neurofibrillary tangles, Pick bodies). These also are not observed in schizophrenia. Finally, reduced numbers of NADPH-d stained neurons in frontal and temporal neocortex are accompanied by increased numbers of stained neurons in the subcortical white matter, suggesting aberrant migration of neurons into neocortical layers. Such subtle anomalies of cortical cytoarchitecture are appealing as a possible neuropathologic substrate of schizo-

phrenia for another reason. They might easily have been overlooked by early neuropathologists, including Kraepelin, who were searching for pathognomonic, degenerative changes.

If the hypothesis that schizophrenia results from anomalous cortical development can be confirmed, then one must next consider what the nature of the developmental defect might be. It seems unlikely that there is a general disruption of the earliest events in cortical maturation. Generalized cortical malformations that result from insults before the sixth fetal week are characterized by reduced cortical surface area, normal or enlarged cortical thickness, and massive neuronal ectopia (Rakic 1988). These findings are not associated with schizophrenia.

Cortical malformations that arise from pathogenetic insults occurring after the sixth fetal week, when the normal number of proliferative units at the ventricular surface is established, are characterized by reduced cortical thickness, ectopic neurons, and in extreme cases, polymicrogyria (Rakic 1988). Cortical pathology in schizophrenia is consistent with an insult during this period of embryogenesis.

Scientific support for structural pathology of medial-temporal-lobe structures (though certainly not conclusive) is currently more substantial than that for prefrontal cortex. However, this may be an artifact of the frequency of studies focusing on the temporal cortex. Nevertheless, a functional abnormality of prefrontal cortex in schizophrenia is supported by a particularly large literature. This combination of findings suggests that the schizophrenic syndrome may be the result of aberrant, horizontal, intracortical connections or synaptogenesis. Considerable pathology of this type could occur before any gross structural, or even microscopic, abnormality would be evident. Anteromedial temporal lobe areas are richly connected to the prefrontal cortex via direct reciprocal connections and via indirect connections through the thalamus (Nauta and Domesick 1982; Weinberger 1993). It may be that temporal and frontal cortex must come "on line" together and process shared information as a neural network, in order that working memory and past experience can be used to guide voluntary behavior (Weinberger 1993). If schizophrenia is a deficit of frontal-temporal neuronal connectivity, it remains for future research to determine if this deficit is truly restricted to a fronto-temporal network, whether selective vulnerability of these cortical areas exists, or whether the syndrome per se reflects dysfunction in this selected network in the context of widespread cortical maldevelopment.

If a developmental abnormality of the brain in schizophrenia is present in early childhood, then the mechanisms that determine the onset of symptomatology in early adulthood also remain to be elucidated. Several possibilities have been proposed including that a mild developmental anomaly of cerebral cortex may interact with another abnormality involving perhaps synaptic pruning, sprouting, or myelinization. However, there does not appear to be much scientific support for this possibility. An alternative explanation is that functional compensation for abnormalities in frontal and temporal cerebral cortex may be possible in early life, but not in later adolescence and adulthood. It may be that the expression of dysfunction of highly evolved prefrontal and limbic cortical areas is not evident until these structures are called upon to cope with the demands of adult social and cognitive functioning. This scenario is also highly speculative, but at least it offers a model by which developmental abnormality of cerebral cortex might account for a clinical illness that until recently did not seem compatible with the neuropathologic data base (for a review see Weinberger 1994).

Emil Kraepelin's clear thinking about a very complex disorder set the stage for the resurgence of research into the neuropathologic accompaniments of schizophrenia. Although current research has proposed a more complex model than the degenerative and localized pathology suspected in Kraepelin's time, we are obliged to recognize Kraepelin's work as the pioneering effort in this field.

References

Akbarian S, Bunney WE, Potkin S, et al (1993a) Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbance of cortical development. Arch Gen Psychiatry 50: 169–177

Akbarian S, Vinuela A, Kim JJ, et al (1993b) Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. Arch Gen Psychiatry 50: 178–187

Altshuler L, Conrad A, Kovelman JA, Scheibel A (1987) Hippocampal cell disorientation in schizophrenia: a controlled neurohistologic study of the Yakovlev collection. Arch Gen Psychiatry 44: 1094–1098

Arnold SE, Hyman BT, Van Hoese GW, Damasio AR (1991) Some cytoarchitectural abnormalities of the entorhinal cortex in schizophrenia. Arch Gen Psychiatry 48: 625–632

Asano N (1967) Pneumoencephalographic study of schizophrenia. In: Mitsuda H et al (eds) Clinical genetics in psychiatry: problems in nosological classification. Igaku Shoin, Tokyo, pp 209–217

Barta PE, Pearlson GD, Powers RE et al (1990) Auditory hallucinations and smaller superior temporal gyral volume in schizophrenia. Am J Psychiatry 147: 1457–1462

Benes FM, Davidson J, Bird ED (1986) Quantitative cytoarchitectural studies of the cerebral cortex of schizophrenics. Arch Gen Psychiatry 43: 31–35

Benes FM, Sorenson I, Bird E (1991) Reduced neuronal size in posterior hippocampus of schizophrenic patients. Schizophr Bull 17: 597–608

Berman KF, Illowsky BP, Weinberger DR (1988) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. IV. Further evidence for regional and behavioral specificity. Arch Gen Psychiatry 45: 616–622

Berman KF, Weinberger DR (1991) Functional localization in the brain in schizophrenia. In: Tasman A, Goldfinger S (eds) American Psychiatric Press Review of Psychiatry, vol 10. American Psychiatric Association Press, Washington, DC, pp 24–59

Berman KF, Torrey EF, Daniel DG, Weinberger DR (1992) Regional cerebral blood flow in monozygotic twins discordant and concordant for schizophrenia. Arch Gen Psychiatry 49: 927–934

Bogerts B, Meertz E, Schonfeldt-Bausch R (1985) Basal ganglia and limbic system pathology in schizophrenia. Arch Gen Psychiatry 42: 784–791

Bogerts B, Falkai P, Haupts M, et al (1990a) Post-mortem volume measurements of limbic system and basal ganglia structures in chronic schizophrenics. Schizophr Res 3:295–301

Bogerts B, Ashtari M, Degreef G, et al (1990b) Reduced temporal limbic structure volume on magnetic resonance images in first episode schizophrenia. Psychiatry Res 35:1–13

Breier A, Buchanan RW, Elkashef A, et al (1992) Brain morphology and schizophrenia. A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. Arch Gen Psychiatry 49:921–926

Broca P (1863) Localisation des fonctions cérébrales: Siège du langage articulé. Bulletin de la Société d'Anthropologie 4:200–203

Brown R, Colter N, Corsellis JAN, et al (1986) Postmortem evidence of structural brain changes in schizophrenia. Arch Gen Psychiatry 43:36–42

Christison GW, Casanova MF, Weinberger DR, et al (1989) A quantitative investigation of hippocampal pyramidal cell size, shape, and variability of orientation in schizophrenia. Arch Gen Psychiatry 46:1027–1032

Cleghorn JM, Zipursky RB, List SJ (1991) Structural and functional brain imaging in schizophrenia. J Psychiatr Neurosci 1653–1674

Colter N, Battal S, Crow TJ, et al (1987) White matter reduction in the parahippocampal gyrus of patients with schizophrenia. Arch Gen Psychiatry 44:1023

Conrad AS, Abebe T, Austin R, et al (1991) Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon. Arch Gen Psychiatry 48:413–417

Davison K, Bagley CR (1969) Schizophrenia – like psychoses associated with organic disorders of the central nervous system. Br J Psychiatry 113 (Suppl 1):18–69

Degreef G, Ashtari M, Bogerts B, et al (1992) Volumes of ventricular system subdivisions measured from magnetic resonance images in first episode schizophrenic patients. Arch Gen Psychiatry 49:531–537

DeLisi LE, Goldin LR, Hamovit JR, et al (1986) A family study of the association of increased ventricular size with schizophrenia. Arch Gen Psychiatry 43:148–153

DeLisi LE, Dauphinais ID, Gershon ES (1988) Perinatal complications and reduced size of brain limbic structures in familial schizophrenia. Schizophr Bull 14:185–191

DeLisi LE, Buchsbaum MS, Holcomb HH, et al (1989) Increased temporal lobe glucose use in chronic schizophrenic patients. Biol Psychiatry 25:835–851

DeLisi L, Hoff AL, Schwartz JE, et al (1991) Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. Biol Psychiatry 29: 159–175

Falkai P, Bogerts B, Rozumek M (1988) Limbic pathology in schizophrenia: the entorhinal region. Biol Psychiatry 24: 515–521

Goldberg TE, Gold JM, Braff DL (1991) Neuropsychological functioning and time-linked information processing in schizophrenia. In: Tasman A, Goldfinger S (eds) American Psychiatric Press Review of Psychiatry, vol 10. American Psychiatric Association Press, Washington, DC, pp 60–78

Gur RE, Mozley D, Resnick SM, et al (1991) Magnetic resonance imaging in schizophrenia. I. Volumetric analysis of brain and cerebrospinal fluid. Arch Gen Psychiatry 48:407–412

Haug JO (1962) Pneumoencephalographic studies in mental disease. Acta Psychiatr Scand 38 (Suppl) 165:1–114

Hecker E (1871) Die Hebephrenia. Arch Pathol Anat Physiol Klin Med 52:394

Heckers S, Heinsen H, Beckmann H (1991) Hippocampal neuron number in schizophrenia. A stereologic study. Arch Gen Psychiatry 48:1002–1008

Huber G (1957) Pneumoencephalographische und psychopathologische Bilder bei endogenen Psychosen. Springer, Berlin Heidelberg New York

Hyde TM, Casanova MF, Kleinman JE, et al (1991) Neuroanatomical and neurochemical pathology in schizophrenia. In: Tasman A, Goldfinger S (eds) American Psychiatric Press Review of Psychiatry, vol 10. American Psychiatric Association Press, Washington, DC, pp 7–23

Iacono WG, Smith GN, Moreau M, et al (1988) Ventricular and sulcal size at the onset of psychosis. Am J Psychiatry 145: 820–824

Ingvar DH, Franzen G (1974a) Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiatr Scand 50:425–462

Ingvar DH, Franzen G (1974b) Distribution of cerebral activity in chronic schizophrenia. Lancet 2:1484–1486

Illowsky BP, Juliano DM, Bigelow LB, Weinberger DR (1988) Stability of CT scan findings in schizophrenia: results of an 8-year follow-up study. J Neurol Neurosurg Psychiatry 51:209–213

Jacobi W, Winkler H (1927) Encephalographische studien an chronisch schizophrenen. Arch Psychiatr Nervenkr 81: 299–332

Jakob H, Beckmann H (1986) Prenatal developmental disturbances in the limbic allocortex in schizophrenics. J Neural Transm 65:303–326

Jeste DV, Lohr JB (1989) Hippocampal pathologic findings in schizophrenia. Arch Gen Psychiatry 46:1019–1024

Johnstone EC, Crow TJ, Frith CD, et al (1976) Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 2:924–926

Kelsoe JR, Cadet JL, Pickar D, et al (1988) Quantitative neuroanatomy in schizophrenia. Arch Gen Psychiatry 45:533–541

Kovelman JA, Scheibel AB (1984) A neurohistological correlate of schizophrenia. Biol Psychiatry 19:1601–1621

Kraepelin E (1919) Dementia Praecox and paraphrenia (transl by Barclay RM; edited by Robertson GM). Facsimile Edition, Krieger, Huntington, NY, 1971

Lemke R (1935) Untersuchung über die soziale Prognose der Schizophrenie unter besonderer Berücksichtigung des encephalographischen Befundes. Arch Psychiatr Nervenkr 104: 89–136

Lichtheim L (1885) On aphasia. Brain 7:433–484

Liddle PF, Friston KJ, Frith CD, et al (1992) Patterns of cerebral blood flow in schizophrenia. Br J Psychiatry 160:179–186

Marsh L, Suddath RL, Higgins N, Weinberger DR (1993) Medial temporal lobe structures in schizophrenia: lack of correlation between size reduction and normal age-related changes. Schizophr Res

Nauta WJH, Domesick VB (1982) Neuronal associations of the limbic system. Neural Basis Behav 10:175–206

Nyback H, Wiesel FA, Berggren BM (1982) Computed tomography of the brain in patients with acute psychosis and in healthy volunteers. Acta Psychiatr Scand 65:403–414

Pakkenberg B (1987) Post-mortem study of chronic schizophrenic brains. Br J Psychiatry 151:744–752

Penfield W, Rasmussen T (1950) The cerebral cortex of man. MacMillan, New York

Rakic P (1988) Specification of cerebral cortical areas. Science 241:170–176

Reveley AM, Reveley MA, Clifford CA, et al (1982) Cerebral ventricular size in twins discordant for schizophrenia. Lancet 2: 540–541

Roberts GW, Colter N, Lofthouse R, et al (1986) Gliosis in schizophrenia. Biol Psychiatry 21:1043–1050

Scheibel AB, Kovelman JA (1981) Disorientation of the hippocampal pyramidal cell and its processes in the schizophrenic patient. Biol Psychiatry 16:101–102

Schulz SC, Koller MM, Kishore PR, et al 81983) Ventricular enlargement in teenage patients with schizophrenia spectrum disorders. Am J Psychiatry 140:1592–1595

Shenton ME, Kikinis R, Jolesz FA, et al (1992) Abnormalities of the left temporal lobe and thought disorder in schizophrenia: a quantitative magnetic resonance imaging study. N Engl J Med 327:604–612

Sponheim SR, Iacono WG, Beiser M (1991) Stability of ventricular size after the onset of psychosis in schizophrenia. Psychiatr Res 40:21–29

Stevens JR (1982) The neuropathology of schizophrenia. Arch Gen Psychiatry 39:1131–1139

Storey PB (1966) Lumbar air encephalography in chronic schizophrenia: a controlled experiment. Br J Psychiatry 112:135–144

Suddath R, Casanova MF, Goldberg TE, et al (1989) Temporal lobe pathology in schizophrenia: a quantitative magnetic resonance imaging study. Am J Psychiatry 146:464–472

Suddath R, Christison GW, Torrey EF, et al (1990) Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. N Engl J Med 322:789–794

Tamminga CA, Burrows GH, Chase TN, Alphs LD, Thaker GK (1988) Dopamine neuronal tracts in schizophrenia: their pharmacology and in vivo metabolism. In: Kalivas PW, Nemeroff CB (eds) The Mesocortical Dopamine System, vol 537. Ann NY Acad Sci, New York

Weinberger DR (1993) A connectionist approach to the prefrontal cortex. J Neuropsychiatry Clin Neurosci 5:241–253

Weinberger DR (1995) Neurodevelopmental perspectives on schizophrenia. In: Bloom F, Kupfer D (eds) Psychopharmacology: a fourth generation of progress. Raven Press, New York, pp 1171–1183

Weinberger DR, DeLisi LE, Neophytides AN, Wyatt RJ (1981) Familial aspects of CT scan abnormalities in chronic schizophrenia patients. Psychiatry Res 4:65–71

Weinberger DR, DeLisi L, Perman GP, et al (1982) Computed tomography in schizophreniform disorder and other acute psychiatric disorders. Arch Gen Psychiatry 39:778–793

Weinberger DR, Wagner RL, Wyatt RJ (1983) Neuropathologic studies of schizophrenia: a selective review. Schizophr Bull 9:193–212

Weinberger DR, Berman KF, Zec RF (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. regional cerebral blood flow evidence. Arch Gen Psychiatry 43:114–124

Weinberger DR, Berman KF, Suddath R, Torrey EF (1992) Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: a magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. Am J Psychiatry 149:890–897

Wernicke C (1874) Der aphasische Symptomencomplex. Cohn and Weigert, Breslau

Wiesel FA, Wik G, Sjogren I, et al (1987) Regional brain glucose metabolism in drug-free schizophrenic patients and clinical correlates. Acta Psychiatr Scand 76:628–641

Young AH, Blackwood DHR, Roxborough H, et al (1991) A magnetic resonance imaging study of schizophrenia: brain structure and clinical symptoms. Br J Psychiatry 158:158–164

Zigun JR, Weinberger DR (1992) In vivo studies of brain morphology in schizophrenia. In: Lindemayer JP, Kay SR (eds) New biological vistas on schizophrenia. Brunner/Mazel, New York, pp 57–81

Zipursky RB, Lim KO, Sullivan EV, et al (1992) Widespread cerebral gray matter volume deficits in schizophrenia. Arch Gen Psychiatry 49:195–205