Limbic-Cortical Neuronal Damage and the Pathophysiology of Schizophrenia

by John G. Csernansky and Mark E. Bardgett

Abstract

Neurobiological studies of patients with schizophrenia suggest that abnormalities of both anatomy and function occur in limbic-cortical structures. An anatomical circuit links the functioning of the ventral striatum (i.e., nucleus accumbens) with the hippocampus and other limbic-cortical structures where neurobiological abnormalities have been found. In animals, lesions of limbic-cortical neurons cause decreases in glutamatergic input to the nucleus accumbens and are also associated with decreases in presynaptic dopamine release, increases in the density of D2-like dopamine receptors, and insensitivity to the actions of dopamine antagonists such as haloperidol. These experiments suggest a plausible pathophysiology of schizophrenia, in that schizophrenic symptoms may be caused by an abnormal dopaminergic state brought about by a primary limbic-cortical lesion and deficits in glutamatergic inputs to the ventral striatum.

Key words: Hippocampus, dopamine, antipsychotic drugs.


The key to improving treatment for many medical illnesses has been to acquire a thorough understanding of pathophysiology. This knowledge, even when the etiology of the illness remains unknown, can effectively guide the development of new therapeutic drugs. The development of an understanding of pathophysiology usually depends on discovering the relationships between the symptoms of illness and normal behaviors or physiology, which are then studied in depth in both humans and animals. Unfortunately, in the case of schizophrenia, we have only begun to develop an understanding of the relationships between hallucinations, delusions, and thought disorder and the normative cognitive phenomena from which these symptoms are probably derived. Moreover, the symptoms of schizophrenia and their underlying cognitive phenomena may be uniquely human and therefore not easily reproduced in animals.

Pathophysiological hypotheses of schizophrenia must therefore be derived and developed in other ways. Substantial advances have been made in determining the neuroanatomical features of schizophrenia, and these characteristics have implicated the involvement of several limbic-cortical and frontal-cortical structures in the disease. In some cases, functional abnormalities can be traced to the same structures, thereby strengthening the evidence for their involvement. We have developed our pathophysiological hypothesis by beginning with the neuronal circuitry most likely involved in schizophrenia and then hypothesized specific ways in which the physiology of neurons within that circuit may be abnormal. We have tested the plausibility of these hypotheses in rodents using the neurotoxin kainic acid to produce the desired anatomical deficits. In an earlier article, we proposed that abnormal arrangements of neurons within the hippocampus might cause functional disinhibition of that structure, thereby increasing excitatory hippocampal inputs to the medium spiny neurons of the nucleus accumbens, which also receive ascending dopaminergic fibers from the ventral tegmental area (VTA) (Csernansky et al. 1991). However, as a result of recent animal experiments in our laboratory, as well as in the laboratories of other research groups, we have modified our hypothesis in several ways. In this article, we present our current hypothesis and the evidence available to support it. Comparisons of our hypothesis with others offered in this issue of the Schizophrenia Bulletin will, we hope, enrich the scientific debate and offer ideas for future research.

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Neuroanatomical Findings in Schizophrenia

In 1976, Johnstone et al. used computerized tomography (CT) to discover that schizophrenia subjects had enlarged ventricular volumes compared with controls. Since that time, much attention has been given to the assessment and interpretation of brain structural abnormalities in schizophrenia and what they may indicate about pathogenetic mechanisms (Crow 1990; Roberts 1990; Cernansky et al. 1991). Many of the most frequently replicated neuroanatomical differences that distinguish schizophrenia patients from normal controls have been found to involve limbic-cortical structures (Roberts 1990). Some (Falkai and Bogerts 1986; Jeste and Lohr 1989) but not all (Heckers et al. 1991) studies of schizophrenia have revealed decreases in the density of hippocampal pyramidal cells. Other investigators have found that hippocampal pyramidal cells are smaller (Benes et al. 1991b) and appear to be abnormally arranged (Kovelman and Scheibel 1984; Conrad and Scheibel 1987; Conrad et al. 1991). Reduced gray matter volume (Altshuler et al. 1990), as well as abnormal cytoarchitecture (Jakob and Beckmann 1986; Arnold et al. 1991), have also been reported within the parahippocampal gyrus. In the anterior cingulate cortex, Benes et al. have found decreased numbers and size of gamma-aminobutyric acid (GABA) interneurons, as well as increases in GABA_A receptor binding on remaining pyramidal cells (Benes and Bird 1987; Benes et al. 1991a, 1992).

In vivo magnetic resonance imaging (MRI) studies have begun to corroborate these findings. For example, Suddath et al. (1989) reported bilateral temporal lobe volume reductions in schizophrenia subjects. However, in twins discordant for schizophrenia, they reported (Suddath et al. 1990) that only the left temporal lobe and left hippocampus in each affected twin was smaller than that of the unaffected cotwin. Hippocampal volume decrements have also been reported in schizophrenia subjects by other groups using in vivo MRI (Bogerts et al. 1990, 1993; Breier et al. 1992; Shenton et al. 1992; Buchanan et al. 1993; McCarley et al. 1993; Rossi et al. 1994). These studies show that the degree of hippocampal volume reduction is relatively small (5%-10%) compared with the error associated with current methods of measurement (Pearson and Marsh 1993).

Shenton et al. (1992) and McCarley et al. (1993) have also reported volume reductions in the parahippocampal gyrus using in vivo MRI. However, Kawazaki et al. (1993) found volume reductions in only the left parahippocampal gyrus compared with controls, suggesting that there may be an exaggerated asymmetry (i.e., L < R) in this brain area (see below). Shenton et al. (1992) and McCarley et al. (1993) have also demonstrated asymmetric volume reductions in the left superior temporal gyrus. Unfortunately, there are as yet no published in vivo MRI studies of the cingulate gyrus, perhaps because of the difficulties involved in making accurate morphometric assessments along its long C-shaped axis.

Not all investigators have reported neuroanatomical irregularities of limbic system structures in schizophrenia. For example, Swayze et al. (1992) found no significant differences in any brain areas of schizophrenia patients compared with normal controls, including the hippocampus, amygdala, and the total volume of the temporal lobe. Also, while Bogerts et al. (1990) found differences in the hippocampal/amygdala volumes of schizophrenia subjects compared with normal controls, these differences were confined to male patients. Finally, DeLisi et al. have found no differences in total temporal lobe volumes (DeLisi et al. 1992) or superior temporal gyrus volumes (DeLisi et al. 1994) between schizophrenia patients and controls.

Neuroanatomical abnormalities have certainly been found in structures outside the limbic system. For example, the frontal lobe, particularly the dorsolateral prefrontal cortex, has been regarded by many investigators (e.g., Weinberger et al. 1992) as a brain area intimately involved in the pathophysiology of schizophrenia. In a postmortem study, Benes et al. (1986) found decreases in the densities of both neurons and glia in the cingulate and motor cortices. More recently, however, Sellem et al. (1995) found increased neuronal densities in the frontal and occipital cortices. In vivo MRI studies show reductions in the total volume of the frontal lobe (Andreasen et al. 1986), the gray-matter volume of the frontal lobe (Zipursky et al. 1992), and the white-matter volume of the frontal lobe (Breier et al. 1992). In addition, a large number of functional imaging studies strongly suggest that energy metabolism is diminished in the frontal lobes of schizophrenia patients (Brodie et al. 1984; Buchsbaum et al. 1984, 1992; Farkas et al. 1984; DeLisi et al. 1985; Wolkin et al. 1985; Kling et al. 1986; Weinberger et al. 1992).

Findings of abnormal anatomy and physiology in the frontal lobes of schizophrenia patients should not be considered in conflict with hypotheses that implicate limbic-cortical structures in the pathophysiology of schizophrenia. There are many interrelationships between limbic-cortical structures within the medial temporal lobe and cingulate gyrus and the frontal lobe (Lopes da Silva et al. 1990) with regard to both anatomy and function, and anatomical abnormalities in one brain area are likely to affect the function of the other. In general, it is unlikely that an abnormality of only one brain structure can explain the presence of schizophrenia in every patient
with the disorder. Rather, it is more likely that abnormal function within a distributed neuronal circuit produces the characteristic symptoms of schizophrenia, and different elements of the circuit may be more obviously affected in one patient or another.

Is Schizophrenia the Result of a Neurodevelopmental or Neurodegenerative Process?

Many characteristics of the neuroanatomical abnormalities found in schizophrenia suggest neurodevelopmental defects that result in a static lesion (Weinberger 1987; Crow 1990). Abnormal arrangements of neurons may be caused by defects in early neuronal migration. Neurons that do not achieve their proper location due to migrational aberrations may then function abnormally or die, and this malfunction or death would be reflected in changes in neuronal size and density (Bloom 1993). However, pathophysiological abnormalities derived from early and static anatomical distortions may appear only later in life, when the involved circuits come under functional demand (Weinberger 1987).

A popular approach to testing the hypothesis that schizophrenia is the result of a neurodevelopmental disturbance has been to study patterns of brain structure symmetry. Asymmetries of brain structure volumes are common, and limbic system structures tend to be smaller on the left than on the right (Geschwind and Levitsky 1968; Galaburda et al. 1987; Galaburda 1991: Bracha 1991). Because the left hemisphere develops over a longer time period than the right hemisphere, environmental insults able to disrupt the development and migration of neurons should have a greater opportunity to affect the left side of the brain, thereby altering normative interhemispheric relationships (Crow 1990).

Several CT and MRI studies support the notion that, in schizophrenia, left-sided abnormalities are more pronounced than right-sided abnormalities (Andreasen et al. 1982; Luchins et al. 1982; Johnstone et al. 1989; Bogerts et al. 1990; see also table 1). Shenton et al. (1992) found volume reductions of the hippocampus only on the left side, and a left-right asymmetry (i.e., \( L < R \)) was found only in the schizophrenia subjects. However, Bartley et al. (1993) found no difference in left-right asymmetries in pairs of monozygotic twins discordant for schizophrenia compared with control twins. Some postmortem studies have also identified abnormalities unique to the left hemisphere, including selective left temporal horn enlargement (Brown et al. 1986; Crow et al. 1989; Heckers et al. 1990) and heterotopic nests of cells within the left parahippocampal gyrus (Jakob and Beckmann 1986).

Unfortunately, in vivo MRI studies comparing the symmetry of specific temporal lobe structures in schizophrenia subjects and controls remain inconclusive. While a majority of studies find volume reductions in limbic system structures in schizophrenia subjects compared with controls, consistent patterns of symmetry or asymmetry have not been demonstrated in either the schizophrenia or control subjects (see table 1). A recent quantitative study of a large number of normals \( (n > 150) \) from age 4 to 18 suggests that \( L < R \) interhemispheric asymmetries are present early in life and stable throughout adolescence and early adulthood, but that they are small in magnitude (3%–5% of structural volumes) (Giedd et al. 1995). Therefore, it is possible that asymmetries in normal subjects and patients with schizophrenia may be too small to be reliably detected using current methods of morphometry and smaller samples.

Irregularities in the shape of brain structures might also be expected to accompany a neurodevelopmental disturbance. There have been frequent suggestions that the gross shape, as well as the volume, of certain brain structures may be abnormal in schizophrenia, in keeping with postmortem studies that find neuronal disarray. For example, Falkai and Bogerts (1986), during their postmortem study of the hippocampus in patients with schizophrenia, observed deformations of its gyral pattern. Similarly, Jakob and Beckmann (1986b) observed unusual gyral patterns on the lateral surface of the temporal lobe. However, these observations have been qualitative, and the degree of anatomical variation among the schizophrenia subjects or the normal controls is not sufficiently understood to permit confident conclusions. Kikinis et al. (1994) have studied the gyral folding pattern on the lateral surface of the temporal lobe in schizophrenia subjects and normal controls using a semiquantitative method. Surface renderings of the sulcal pattern were obtained by computer algorithm and were then visually evaluated on a 0–4 scale by four expert raters blind to the diagnosis. The results of this study were in general agreement with previous qualitative work and showed that the schizophrenia subjects demonstrated vertical sulcal patterns more often than the normal controls. In future research, fully quantitative analysis of brain shape characteristics will be needed to better define the nature of the anatomical abnormality.

Evidence of neurodevelopmental irregularities does not rule out the possibility of a later progressive lesion. Current in vivo neuroimaging technologies may not offer sufficient precision to detect gradual decreases in brain structure volumes on the order of 1 to 2 percent per year (Pearlson and Marsh 1993). In Alzheimer’s disease, where rapidly progressive, and larger reductions in the volume of the hippocampus and other limbic-cortical structures are common, time periods of 2 or more years are still
Table 1. Magnetic resonance imaging studies of brain asymmetry in schizophrenia

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Note—Side-to-side differences were considered present only when differences were greater than 5 percent; such differences may or may not have been statistically significant. Cont or C = control subjects; Schiz or S = schizophrenia subjects; Comp = group comparison; HIPP = hippocampus; AMYG = amygdala; PARHIPP = parahippocampal gyrus; STG = superior temporal gyrus; L = left; R = right; and ND = not different.

¹In these studies, the anterior hippocampus and amygdala were assessed together.
²In this study, the measurements were averaged areas from several contiguous slices.
³In this study, the schizophrenia group was composed of concordant siblings.
needed to detect the reduction using high-resolution MRI (Fox et al. 1996). Early lesions due to neurodevelopmental irregularities may result in brain structures that are more vulnerable to damage via other mechanisms later in life, such as excitotoxicity or apoptosis (Margolis et al. 1994; Olney and Farber 1993). Final resolution of the nature of limbic-cortical neuronal damage in schizophrenia (i.e., static versus progressive) must await more sensitive methods for in vivo neumorphometric assessment. Nonetheless, current findings suggest that there are limbic-cortical abnormalities in at least a subgroup of patients with schizophrenia, and that such abnormalities are present early in the progression of the disorder.

Functional Consequences of Limbic-Cortical Dysfunction

Even given the characteristics of neuroanatomical abnormalities found in schizophrenia to date, there are still questions regarding the functional abnormalities that might arise from such abnormalities. In figure 1, the functional interrelationships of the hippocampus, frontal cortex, and basal ganglia are diagrammed. Of particular note is the interplay of excitatory hippocampal projections from the hippocampus (Walaas and Fonnum 1980) and other limbic-cortical structures (Sesack et al. 1989) to the shell of the nucleus accumbens, when they interact with ascending dopaminergic projections from the VTA. Complementing the neuroanatomical findings reviewed above, a number of functional studies in both humans and animals now suggest that there are physiological abnormalities of limbic-cortical structures and that these abnormalities may involve decreases in the excitatory limbic inputs into ventral basal ganglia structures.

First, an increasing number of research groups have demonstrated that important clinical correlates of limbic system neuroanatomical abnormalities are observed in schizophrenia. For example, in a sample of predominantly never-treated patients, Degreaf et al. (1992) reported that enlargement of the temporal horn of the lateral ventricle was correlated with increasing severity of both positive and negative schizophrenic symptoms before neuroleptic treatment. Further, this group reported a correlation between decrements in total mesiotemporal lobe volumes and increasing severity of positive, but not negative symptoms, in a group of more chronic subjects (Bogerts et al. 1993). Shenton et al. (1992) have reported that the severity of formal thought disorder after neuroleptic treatment was correlated with decreased volume of the left superior temporal gyrus. Superior temporal gyrus volume reductions have also been correlated with the presence of auditory hallucinations (Barta et al. 1990). However, Zipursky et al. (1994) were not able to demonstrate correlations between the volume of the superior temporal gyrus and the severity of any symptom grouping assessed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). Attempts to correlate the severity of symptom groupings after neuroleptic treatment with structural variables may be problematic, since one may confound the severity of symptom groupings before treatment with the capacity of such symptom groupings to respond to neuroleptic treatment. Using other approaches to the in vivo assessment of limbic-cortical function, there have been correlations between the reduction of brain structure volume and deficits in both cognitive and psychophysiological (e.g., evoked P300 amplitude) measures (McCabe et al. 1993; Nestor et al. 1993; Seidman et al. 1994).

Another approach to understanding the functional consequences of limbic-cortical neuropathology in subjects with schizophrenia has been to study the effects of phencyclidine (PCP) and other noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists in both humans and animals. PCP binding sites on NMDA receptors are densely expressed within the hippocampus and other limbic areas (Lopes da Silva et al. 1990), and noncompetitive blockade of NMDA receptors by administration of PCP may mimic some types of limbic-cortical neuropathology. In human subjects, ketamine administration causes amnesia and other deleterious cognitive effects (Krystal et al. 1994), and PCP administration causes psychotic symptoms that resemble some symptoms of schizophrenia (see Javitt and Zukin [1991] for review). Olney and Farber (1995) have recently suggested that NMDA receptor hypofunction plays a central role in the pathophysiology of schizophrenia. Specifically, they proposed that damage to limbic-cortical neurons in the cingulate cortex may occur when NMDA receptor hypofunction fails to provide the tonic stimulation of cortical GABA interneurons that provide protective inhibition to cortical pyramidal neurons. In line with this hypothesis, Benes et al. (1991a, 1992) have reported evidence consistent with the dysfunction of GABA interneurons within the cingulate cortex.

Other animal models of damage to limbic-cortical neurons are under intense investigation, with particular attention being paid to the consequences of such damage for subcortical dopaminergic function. As diagrammed in figure 1, subicular terminals within the hippocampus send glutamatergic efferents to the nucleus accumbens (Walaas and Fonnum 1980), so hippocampal damage should reduce accumbens glutamate levels and function. Indeed, glutamate concentrations in the nucleus accumbens and septum have been found to be reduced after complete hippocampal extirpation (Nitsch et al. 1979) and after bilateral (Zaczek et al. 1979), but not unilateral (Jaskiw et al. 1991), fornix transections. After kainic acid-induced par-
Numerous neuroanatomical connections link the ventral striatum (i.e., nucleus accumbens) with the hippocampus and other limbic-cortical structures. These projections to the nucleus accumbens are primarily glutamatergic. In the nucleus accumbens, these glutamatergic projections are functionally linked with ascending dopaminergic pathways from the ventral tegmental area. In addition, projections from limbic-cortical areas may alter the firing rates of dopamine neurons in the ventral tegmental area. D2-like postsynaptic dopamine receptors in the nucleus accumbens are thought to be an important site for antipsychotic drug action. CA = cornu ammonis.
tial damage to the hippocampus (see below), we have observed reductions in potassium-stimulated, but not basal, levels of glutamate release in the nucleus accumbens (Bardgett et al. 1995a).

Since dopamine release within the nucleus accumbens may be altered by glutamate released from nearby limbic-cortical afferents (O'Donnell and Grace 1994, 1995; see also Grace 1991 for a review), reductions of glutamatergic input to the nucleus accumbens caused by limbic-cortical neuropathology should have important consequences for dopamine function. In addition, subcortical dopamine release may be altered by changes in the activity of limbic-cortical projections onto VTA dopamine neurons (Taber et al. 1995). A variety of studies have assessed the impact of gross hippocampal damage on subcortical dopaminergic function. In an early study of rats, Springer and Issacson (1982) observed transient decreases in dopamine concentrations in the nucleus accumbens following complete hippocampal ablation. However, Lipska et al. (1991), using ibotenic acid to produce focal hippocampal damage, reported that dorsal hippocampal lesions did not alter dopamine turnover in the accumbens at 14 and 28 days after surgery. In a subsequent report (Lipska et al. 1992), these authors found that dopamine concentrations in the nucleus accumbens were increased at 14 days but were decreased at 28 days following a similar lesion in the ventral hippocampus. Also, in this study, elevated norepinephrine concentrations and decreased dihydroxyphenylacetic acid and homovanillic acid (HVA) concentrations were observed in the medial prefrontal cortex at 28 days, while concentrations of norepinephrine or dopamine and its metabolites in the corpus striatum were unaffected at 14 or 28 days. Interpretation of these studies merits caution since extensive hippocampal lesions were employed. Lesions were nonselective with respect to pyramidal cell subfields of the cornu ammonis (CA1)–4, lesions did not affect the hippocampus along its entire septotemporal axis, and tissue damage may have involved fibers of passage and extrahippocampal tissue, in addition to intrinsic hippocampal neurons.

Animal studies involving partial or graded forms of neuronal loss in limbic-cortical structures may offer more valid insights into the issue of hippocampal perturbation and its effects on subcortical dopaminergic function. Epileptiform activity induced by kindling of the amygdala or hippocampus produces partial neuronal degeneration within these structures (Sutula et al. 1988; Cavazos and Sutula 1990), and several years ago we (Csermanky et al. 1988a, 1988b) showed that increases in dopamine D2 receptor binding and turnover in the nucleus accumbens also occur after limbic-cortical kindling. The persistence of kindling-induced changes in subcortical dopaminergic systems (Csermanky et al. 1988b; Janowsky et al. 1991) suggests that neuroanatomical alterations in limbic-cortical structures, rather than transient electrophysiological changes, underlie this phenomenon.

Nadler et al. (1978) first demonstrated that graded damage to hippocampal neurons can be reliably obtained after slow intracerebroventricular (ICV) administration of kainic acid. The hippocampus is selectively vulnerable to the neurotoxic effects of excitatory amino acids, especially kainic acid (Olney et al. 1974), because of the high density of kainate-type glutamate receptors in the CA3 region of the hippocampus (Foster et al. 1981; Werner et al. 1991). In addition, dispersion of kainic acid throughout the lateral ventricle permits lesioning of the hippocampus along its entire septo-temporal length, though most neuronal loss has been found in septal regions (Jarrard 1982). Since ICV injection of kainic acid produces a disproportional loss of CA3/CA4 neurons, the inner third of the molecular layer of the dentate gyrus, and the striatum radiatum and stratum oriens of CA1 are denervated. Reinnervation occurs in both the dentate and CA1 areas within days after kainic acid infusion, and redundant cell connections may develop (Tauck and Nadler 1985). In the CA1 region of the kainic acid-lesioned animal, synaptic density returns to near-normal levels around 40 to 50 days postlesion, and these newly formed synapses appear to originate from axon collaterals of nearby CA1 pyramidal cells (Nadler et al. 1980).

Neuronal regrowth after ICV administration of kainic acid may have its own functional consequences, since long-term CA1 hyperexcitability and synchrony develop after kainic acid lesions (Tauck and Nadler 1985; Nakajima et al. 1991). Hippocampal damage induced by kindling or intense afferent stimulation probably induces a similar sequela of regrowth and abnormal electrical activity in the hippocampus (Cavazos et al. 1991; Sloviter 1991). These phenomena may be pertinent to the pathophysiology of schizophrenia, since aberrant reinnervation has been proposed as a likely feature of the disease (Stevens 1992). In addition, damage to other limbic-cortical brain structures may slowly continue after administration of kainic acid, due to apoptotic mechanisms (see Charriaut-Marlangue et al. 1996 for review).

Relative to other putative animal models of schizophrenia, kainic acid-induced limbic-cortical damage may have more significant advantages. First, the moderate level of hippocampal cell loss observed in both kainic acid-induced lesions (Foster et al. 1981; Werner et al. 1991) and schizophrenia has been observed to be more severe in the septal or anterior regions of CA3/CA4 (Jeste and Lohr 1989). Second, the intense axonal sprouting that occurs in the CA1 region of the kainic acid-lesioned hippocampus may reproduce aspects of the hippocampal axonal disarray observed by some investigators (Kovelman and
Scheibel 1984; Conrad and Scheibel 1987; Conrad et al. 1991) and the pathological reinnervation proposed by Stevens (1992). Third, a loss of hippocampal kainate receptors (Kerwin et al. 1990) has been found in the post-mortem hippocampus of schizophrenic brains and in the kainic acid-lesioned animal (Bardgett and Csernansky, unpublished data). Finally, kainic acid lesions in rats are associated with changes in subcortical dopamine function, such as increases in dopamine D1-like receptor binding (Bardgett et al. 1995b); increased behavioral sensitivity to stress, dopamine agonists, and NMDA receptor antagonists (Bardgett et al. 1995c); and decreases in dopamine release in the nucleus accumbens following potassium stimulation (Bardgett et al. 1995a).

Findings of a disturbed dopamine system following kainic acid-induced limbic-cortical damage support and extend the hypotheses of Carlsson (Carlsson and Carlsson 1990), Grace (1991), and our own group (Csernansky et al. 1991). Figure 2 summarizes the hypothesized relationship between disturbed glutamate function and disturbed dopamine function as it might occur both in the kainic acid-lesioned animal and in subjects with schizophrenia. Decreased glutamatergic input from the hippocampus and limbic cortex to the nucleus accumbens is coupled to the decreased presynaptic availability of dopamine and an increase in postsynaptic dopamine receptors. Changes in dopaminergic function as formulated in this hypothesis would support the proposal that some human behaviors (e.g., volition) linked to subcortical dopamine function would be blunted in schizophrenia, but that a sudden reversal of behavior in the form of excitement and increased sensitivity to sensory stimulation could occur if stress-induced increases in dopamine release were combined with increased sensitivity of postsynaptic dopamine receptors (Csernansky et al. 1991).

Clinical Heterogeneity and Responses to Antipsychotic Drugs

Patients with schizophrenia may be categorized according to criteria other than those related to symptom severity. It is well known that schizophrenia patients are also heterogeneous in their responses to antipsychotic drugs, and this variability is not easily predicted by common clinical features (Csernansky et al. 1985; Stern et al. 1993). Heterogeneity in the response to typical and atypical antipsychotic drugs poses a serious treatment dilemma. With the availability of clozapine for the treatment of patients who fail to respond to typical antipsychotics, the ability to identify potential clozapine responders before a useless series of trials of other drugs has been undertaken is essential. However, clinical characteristics are also not helpful in predicting the capacity to respond to clozapine (Kane et al. 1988; Stern et al. 1993).

The specific mechanisms of action whereby neuroleptic drugs exert their therapeutic benefits for patients with schizophrenia remain unknown. Friedhoff (1988) has hypothesized that reactivity of subcortical dopaminergic synapses to neuroleptics is essential for efficacy. During neuroleptic treatment of schizophrenia patients, plasma HVA (pHVA) concentrations first rise and then fall, and this pattern of change in pHVA has become regarded as a reliable predictor of a successful response to neuroleptic drugs (Stern et al. 1993). Bowers and coworkers first showed that schizophrenia patients can be divided on the basis of whether or not pHVA concentrations change in this way during neuroleptic treatment (Bowers and Heninger 1981), and suggested that neuroleptic responders (i.e., patients whose positive symptoms decrease during treatment) demonstrate initial increases and later decreases in pHVA during neuroleptic treatment, while patients who are refractory show little change in pHVA.

Implication of Limbic-Cortical Neuropathology for Understanding the Heterogeneity of Patients With Schizophrenia

As mentioned above, the abnormal anatomy and function of any one brain area is unlikely to produce the diverse symptoms of schizophrenia. It would also be naive to suggest that the symptoms are the same and are produced by a single mechanism in all schizophrenia patients. Schizophrenia symptoms have been recently divided into three categories—psychotic symptoms, disorganized symptoms, and negative symptoms—and the validity of these psychopathology subfactors in schizophrenia subjects at different phases of their illness has been demonstrated (Andreasen et al. 1995; Arndt et al. 1995). Given
Figure 2. Interactions within a limbic-cortical circuit after hippocampal neuronal loss

Limbic-cortical neuropathology should have consequences for the function of various cortical and subcortical structures. Following limbic-cortical neuronal loss, decreases in glutamatergic input to the ventral striatum (i.e., nucleus accumbens) occurs. This loss of glutamatergic stimulation may also be associated with decreases in presynaptic availability of dopamine and corresponding increases in postsynaptic dopamine receptor sensitivity in the nucleus accumbens (note increases in dopamine receptor density compared with figure 1). CA = cornu ammonis.
(Bowers and Hninger 1981; Bowers et al. 1984, 1987). These findings were later replicated by Pickar et al. (1984, 1986), who also demonstrated a strong relationship between the timing of phVA decreases and the disappearance of psychotic symptoms. Since the mid 1980s, many groups (Davila et al. 1988; Sharma et al. 1989; Chang et al. 1990; Petrie et al. 1990; Davidson et al. 1991; Mazure et al. 1991), but not all (van Putten et al. 1989; Javadi et al. 1990), have replicated these findings in a variety of populations of schizophrenia subjects.

Various hypotheses have been proposed to explain why phVA concentrations change in this manner during successful responses to antipsychotic drugs. All these hypotheses depend on the assertion that phVA levels parallel levels of dopamine release and metabolism in one or more brain areas (Stern et al. 1993). Initial increases and later decreases in indices of dopamine release and metabolism have been observed during antipsychotic drug administration in multiple areas of rat brain, including the caudate putamen, nucleus accumbens, and olfactory tubercle (Asper et al. 1973; Sayer et al. 1975; Bowers and Hoffman 1986; Chang et al. 1986; Csernansky et al. 1990, 1993). The mechanisms responsible for these changes in dopamine turnover during neuroleptic drug administration may involve parallel changes in the rate of dopaminergic neuronal firing (Bunney 1988) and in the density or function of dopamine terminal autoreceptors (Bannan et al. 1980; Scatton 1980; Nowak et al. 1983; Saller and Sallam 1985).

Extending this area of research, we have recently found that normal glutamatergic input from limbic-cortical areas to subcortical structures may be necessary for normal dopaminergic responses to antipsychotic drug administration (Salaris et al. 1995; Bardgett and Csernansky 1996). In kainic acid-lesioned rats, the usual increases in dopamine turnover are not observed after acute treatment with haloperidol. However, after clozapine treatment, increased dopamine turnover following acute administration was observed (Bardgett et al. 1997). In addition, we have observed that the ability of haloperidol, but not clozapine, to block dopamine agonist-induced hyperlocomotion is impaired following kainic acid lesioning of limbic-cortical neurons (Bardgett and Csernansky 1996). These experiments suggest that damage to the efferents from limbic-cortical structures that make functional connections with ascending dopaminergic fibers may cause dopaminergic projections and their synaptic targets within the nucleus accumbens to function abnormally. Moreover, these experiments suggest that abnormalities in limbic-cortical projections to the nucleus accumbens may cause insensitivity to typical, but not atypical, antipsychotic drugs.

If a failure of dopaminergic pathways to respond to the presence of antipsychotic drugs is associated with an insensitivity to the clinical effects of some antipsychotic drugs, then the presence of limbic-cortical neuropathology, perhaps observable using in vivo MRI, should be an important predictor of the capacity for antipsychotic drug responses in schizophrenia patients. In regard to this hypothesis, it is worth noting that correlations between the severity of psychotic and disorganized symptoms and limbic-cortical structural abnormalities have often been reported after treatment with antipsychotic drugs. Therefore, it may be that the capacity for antipsychotic drug responses, as well as the original severity of the symptoms, is correlated with limbic-cortical neuroanatomical deficits.

In figure 3, a possible relationship between the degree of limbic-cortical neuropathology and both the appearance of schizophrenic psychopathology and the capacity for antipsychotic drug responses is diagrammed. Rather than showing clinical symptomatology and antipsychotic drug responses as unrelated phenomena, we suggest that they may occur on a physiological continuum. The capacity of antipsychotic drugs to correct abnormal physiological states and reverse related forms of psychopathology may depend on the relative intactness of circuits and mechanisms that are ordinarily responsible for producing and modulating corresponding behaviors. In other words, if a particular neuronal circuit is involved in the processing of perceptual information, dysfunction of that circuit caused by loss or damage to its neuronal elements would first produce corrected hallucinations, and then, as the degree of anatomical damage and dysfunction is increased, hallucinations that are uncorrectable by any form of pharmacological manipulation. An analogy to this phenomenon is the degree to which levo-dopa can correct basal ganglia dysfunction due to the death of substantia nigra dopamine neurons in patients with Parkinson's disease. When the degree of neuropathology is mild, symptomatic relief can be obtained by augmenting dopamine synthesis and release from the terminals of remaining dopamine neurons. However, when the remaining neurons become too few, the clinical pathology becomes more enduring and levo-dopa treatment loses efficacy. In the case of schizophrenia, we propose that it is the function, and possibly the number, of limbic-cortical neurons that may be correlated with clinical pathology and resistance to treatment with typical antipsychotic drugs.

Summary

After a synthesis of anatomical and functional studies of schizophrenia patients and after considering the implica-
Figure 3. Relationship between increasing damage to neuronal circuits and clinical phenomenology

Severity of Psychopathology and Responsivity to Treatment

Clinical psychopathology and the capacity to respond to typical antipsychotic drugs may occur on a physiological continuum in relationship to the degree of limbic-cortical neuropathology.

Tions of various animal models of schizophrenialike limbic-cortical neuropathology, a hypothesis concerning the pathophysiology of schizophrenia is proposed. As previously proposed by Carlsson and colleagues (Carlsson and Carlsson 1990), reduced excitatory glutamatergic inputs from the hippocampus and other limbic structures to the ventral striatum is a key feature of this hypothesis and may result in the appearance of clinical symptoms, particularly psychosis and thought disorganization. Negative symptoms, in turn, are more likely to result from the abnormal functioning of frontal lobe structures, in particular those structures (e.g., dorsolateral prefrontal cortex) that receive extensive anatomical connections from limbic structures. In addition, damage to limbic-cortical structures may predict a reduced capacity to respond to typical antipsychotic drugs such as haloperidol. The response to clozapine may depend on the integrity of other neuronal circuits.

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Announcement

The Sixth World Congress on Psychiatric Genetics will be held in Bonn, Germany, October 7–10, 1998. The Congress will include oral presentations, posters, plenary talks, and workshops in all fields of psychiatric genetics.

The following topics will be presented: basic neurobiological mechanisms in the central nervous system, animal models of mental disorders, genetic epidemiology, genetic factors in autism, schizophrenia, affective disorder, alcoholism, addiction, tourette syndrome, mental subnormality, dementia, and other disorders.

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