

# The Biological Basis of Schizophrenia: New Directions

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The desire to understand the pathophysiology of schizophrenia has inspired an explosion in research over the past decade. This review highlights some key studies that have led to fundamental changes in our understanding of this disorder, focusing on the search for genes in schizophrenia, as well as several recent alternatives to the original dopamine hypothesis of schizophrenia. Advances in genetic methodology have allowed schizophrenia researchers to conduct genome-wide searches for susceptibility genes. Although these studies have identified several regions that demonstrate potential linkage with schizophrenia, a definitive genetic cause has not yet been proved. Recent neurochemical hypotheses have focused on the cortical amino acid neurotransmitter systems (i.e., glutamate and GABA), while anatomical studies suggesting abnormal brain development and premorbid functional deficits have led some researchers to propose a neurodevelopmental origin for schizophrenia. A sizeable database can be marshaled in support of each of these ideas, but none as yet fully explain the biological basis of schizophrenia.

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The biological foundation of schizophrenia is a complex and evolving concept. Among the exciting areas of recent neuropsychiatric research, three stand out: (1) the search for genes; (2) the increasing interest in the potential etiologic role of amino acid neurotransmitters; and (3) the neurodevelopmental hypothesis of schizophrenia. This review represents a critical appraisal of progress in each of these three areas and attempts to offer insights into future research directions for understanding the biology of schizophrenia.

## THE SEARCH FOR SUSCEPTIBILITY GENES

The availability of highly polymorphic DNA markers has made it possible to scan the human genome with very high resolution and reliability for sites potentially linked to schizophrenia. Several studies utilizing these highly polymorphic markers have implicated a number of chromosomal regions that fulfill statistical criteria for linkage in several different pedigrees around the world, suggesting that schizophrenia is a multifactorial disease with a complex mode of inheritance.<sup>1-7</sup> The potential susceptibility

loci for schizophrenia identified so far reside on the long arm of chromosome 22 (22q12-13),<sup>1</sup> and the short arms of chromosomes 3 (3p26-24),<sup>3</sup> 5 (5p13),<sup>5</sup> 6 (6p24-22),<sup>2,7</sup> 8 (8p22-21),<sup>2,3</sup> 9 (9p23),<sup>3</sup> and 20 (20p12).<sup>3</sup> All of these regions have shown genetic linkage with schizophrenia in one or more studies. However, the levels of significance tend to be low, and the effect sizes of these genetic linkage results are quite small (i.e., minor gene effect across families or a genetic factor in only a small percentage of families).<sup>8</sup> In addition, a number of studies have been unable to replicate the genetic linkage findings; this failure may be due to differences in the pedigrees or the use of different genetic markers located on the same chromosome.<sup>8,9</sup>

The DNA sequences captured in genetic studies using polymorphic markers have not yet been characterized. Moreover, the genes contained within these large regions of DNA sequences are only partially known, and it is not clear which, if any, of these genes are related to schizophrenia. For example, the region 6p24-22 on the short arm of chromosome 6, which has been linked to schizophrenia in several pedigrees,<sup>2,7</sup> contains over 200 genes, including the genes for prolactin, argininosuccinate synthetase, and insulin. However, the role that any of them play in schizophrenia is unknown. Similarly, regions on other chromosomes showing linkage with schizophrenia also contain cloned genes in the vicinity of the described susceptibility locus. The majority of these cloned genes appear unlikely to encode schizophrenia. A primary goal of future research, therefore, will be to determine if the schizophrenia locus represents a previously cloned gene, a gene yet to be cloned in one of the candidate regions, or the product(s) of one or more genes from this region that increase the risk of developing schizophrenia.

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Association findings, in contrast to linkage findings, are not based on a genetic model of transmission, but rather describe variations in a particular genetic allele that are associated with the disease more often than would be predicted by chance alone. Such allelic variations reported in schizophrenic patients include the 5-HT<sub>2A</sub> receptor site<sup>10,11</sup> and the dopamine D<sub>3</sub> receptor site.<sup>12</sup> Like linkage studies, some of these findings have not been replicated in different patient populations, suggesting that allelic variations may only play a restricted role in certain patients.<sup>13</sup> A final genetic abnormality, reported in 1994 by St. Clair, is an abnormal number of trinucleotide repeats (CAG repeats),<sup>6</sup> similar to the genetic defect identified in Huntington's disease. However, like the other genetic studies described above, this finding has not been replicated in all pedigrees.<sup>4,14</sup> Obviously, these issues require further study.

Overall, recent advances in the genetic origins of schizophrenia suggest the existence of multiple genes, each of which conveys a small amount of liability, meaning that the disorder itself is an additive genetic phenomenon. To test this hypothesis, it will be vital to determine the susceptibility phenotype. In other words, what do genes contributing to increased susceptibility actually do to make a person susceptible? One possibility is that certain subclinical phenotypes—such as aspects of personality, eye tracking, cognitive function, and sensory gating—are closely linked to the susceptibility effect of these genes, perhaps more closely than are the diagnostic symptoms.<sup>15–17</sup> Progress in genetics has brought us closer to solving the genetic mystery of schizophrenia, but at the same time has raised new questions that will need to be answered before we fully understand its genetic origins.

### **AMINO ACID NEUROTRANSMITTER HYPOTHESES**

In contrast to the classic dopamine hypothesis of schizophrenia, recent theories about the neurochemical mechanisms underlying the disorder have emphasized a potential primary role of amino acid neurotransmitters. Aided by the development of improved pharmacologic tools for studying these transmitter systems, this shift in focus has been largely driven by a growing recognition of the important role of the cerebral cortex—and hence, its two principal neurotransmitters, glutamate and gamma-aminobutyric acid (GABA)—in the neuropathology of schizophrenia. In addition, new data suggest that some of the recently introduced atypical antipsychotic drugs (e.g., clozapine, olanzapine) may have effects on behaviors mediated by amino acid neurotransmitters.

#### **Glutamate**

Glutamate, the principal excitatory neurotransmitter in the brain and the amino acid neurotransmitter of corti-

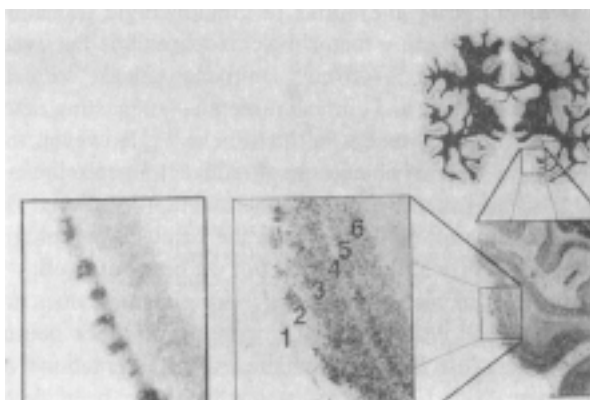
cofugal and intracortical projection neurons, has been the most intensely studied of the amino acid transmitters in the past several years. Perhaps the most compelling argument to implicate alterations in glutamatergic transmission as a contributing factor in schizophrenia is the overwhelming evidence—from neuroanatomical studies, functional studies, and clinical research—suggesting cerebral cortical involvement in this illness.<sup>18–24</sup> However, the question of whether changes in glutamate transmission are responsible for the cortical malfunction observed in schizophrenia or, conversely, are the result of pathologic changes in cortical function has not yet been resolved.

A role of increasing importance for glutamate does not preclude the involvement of dopamine or other neurotransmitters. In fact, well-characterized interactions of glutamate with GABA and dopamine have been demonstrated in animal models.<sup>25</sup> Considering the density of cortical connections with striatal and midbrain regions, interactions between glutamate, dopamine, and GABA systems would not be surprising.

The clinical effects of glutamate receptor antagonists such as PCP, ketamine, and MK-801 provide a second line of evidence in support of a glutamate hypothesis. For example, individuals taking ketamine or PCP exhibit high scores on the Brief Psychiatric Rating Scale (BPRS), suggesting a drug-induced model of schizophrenia.<sup>26</sup> However, these subjects also display abnormally high scores on dissociative phenomenon rating scales, decreasing the specificity of this model.

Yet another area of interest has been the search for post-mortem markers of glutamate malfunction, particularly glutamate receptors. The complexity of glutamate receptor systems not only affords considerable plasticity, an essential characteristic for a highly evolved cortical neurotransmitter system involved in learning and memory, but also offers multiple loci for potentially relevant alterations in receptor number, density, or molecular structure. Each of the four classes of glutamate receptors—the NMDA, the AMPA, the kainate, and the metabotropic receptors—are derived from distinct gene families encoding a variety of subunits that can form various receptor/channel combinations with a range of characteristics. To date, radioligand binding studies in postmortem tissue from schizophrenic patients have examined the kainate, AMPA, and NMDA receptors.<sup>22,27,28</sup> While the results of these studies are not entirely consistent, in general, they tend to show decreased binding to kainate receptors in the limbic cortex, particularly the hippocampus, and increased binding to AMPA and NMDA receptors in the prefrontal cortex. One interesting study, recently reported by Akbarian and colleagues,<sup>18</sup> measured mRNA coding for five NMDA receptor subunits (NR1, NR2A–D) in cortical tissue and found no significant differences between schizophrenic patients and controls, although relative increase in the NR2D subunit in the prefrontal cortex was noted. Unfortunately, the

**Figure 1.**  $^{125}\text{I}$ -Neurotensin Binding Sites in Entorhinal Cortex of Normal (center panel) and Schizophrenic (left panel) Patients\*



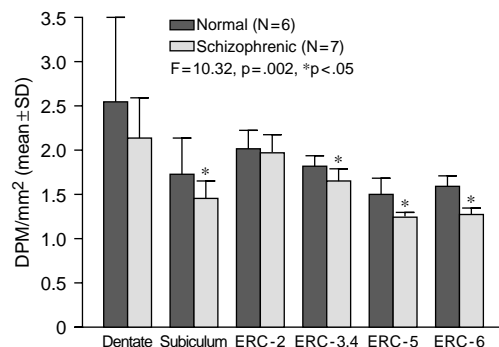
\*The left and center panels are magnified views of the boxed region in the sections depicted to the right; entorhinal layers 1–6 are denoted in the center panel.

overall levels of expression of the NMDA subunits were low and the statistical results were not corrected for the multiple tests performed, casting some doubt on the overall validity of the results.

Our laboratory has used several other approaches to look for alternative tissue markers of glutamatergic neurons. For example, we examined neurotensin receptors expressed by a selective population of glutamatergic neurons in the entorhinal cortex,<sup>29</sup> a region of the brain that has demonstrated possible developmental abnormalities in schizophrenia. This study, using quantitative receptor autoradiography with  $^{125}\text{I}$ -iodo-neurotensin, demonstrates a reduction in the density of receptors in layer II of the entorhinal cortex (Figure 1), consistent with an abnormality in the peptidergic regulation of this population of glutamate neurons. Cholecystikinin (CCK) is a second neuroactive peptide that is co-localized with glutamatergic neurons. In an attempt to further investigate reports over the past 15 years that CCK-immunoreactivity is reduced in the temporal lobe of schizophrenics, Bacchus et al. used *in situ* hybridization to look at the expression of CCK mRNA in the entorhinal cortex (Figure 2).<sup>30</sup> Unlike the changes in neurotensin receptors, which were selective for afferent side projections from entorhinal cortex to hippocampus, the reductions found by Bacchus and coworkers in CCK mRNA expression localized to the efferent projections from the hippocampus in the deep layers III–VI. This suggests some disconnection, at the neurochemical level, of the hippocampus from the entorhinal cortex. This result has been recently confirmed by another group.<sup>31</sup>

Another approach to evaluating glutamate function involves measuring the activity of an intraneuronal enzyme, N-acetyl-alpha-linked acidic dipeptidase (NAALADase), concentrated in glutamate neurons and responsible for cleaving N-acetylaspartylglutamate (NAAG) to N-acetyl

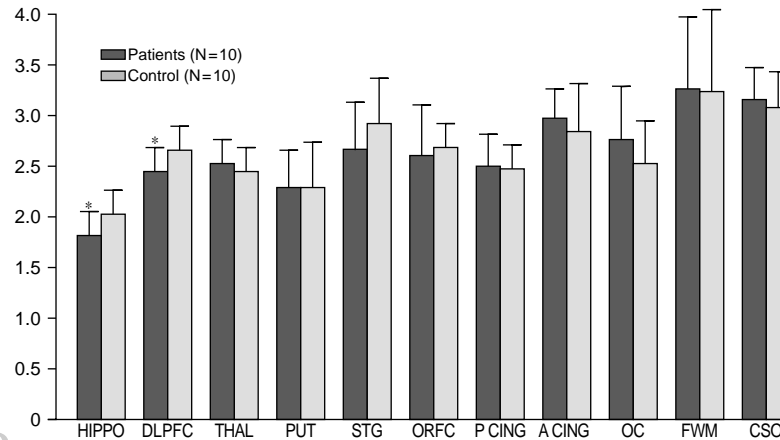
**Figure 2.** CCK mRNA in Entorhinal Cortex\*



\*Adapted from reference 30, with permission.

aspartate (NAA) and glutamate. A recent paper published by Tsai et al.<sup>23</sup> found increased levels of NAAG in conjunction with decreased NAALADase activity and glutamate levels in the hippocampus and prefrontal cortex of patients with schizophrenia. In addition, *in vivo* neurochemical studies have taken advantage of the unique proton magnetic resonance properties of N-acetyl-containing chemical moieties, such as NAA. The second largest peak in the proton spectra, NAA can be assayed *in vivo* using NMR spectroscopy. Using large single-voxel proton magnetic resonance spectroscopy ( $^1\text{H}$ -MRS), Yurgelun-Todd et al. have reported reductions of NAA in the temporal lobe.<sup>32</sup> Our group used a recently introduced modification of the  $^1\text{H}$ -MRS imaging technique ( $^1\text{H}$ -MRSI) that allows the simultaneous acquisition of proton spectra from voxels in multiple brain regions to document highly localized decreases in NAA in the rostral hippocampus and the dorsolateral prefrontal cortex of schizophrenic patients, compared to controls (Figure 3).<sup>20</sup> These data are in agreement with the results of postmortem assays of NAALADase activity and suggest that the neurochemical pathology reflected by the NAAG/NAALADase/NAA pathway is regionally specific in schizophrenia.

Other evidence, however, argues against certain elements of what might be called “the glutamate hypothesis of schizophrenia.”<sup>22</sup> For example, while it has been suggested that the pathophysiology of schizophrenia can be explained by a progressive excitotoxic process involving glutamate,<sup>22</sup> long-term clinical deterioration is not consistently correlated with the progression of neuropathologic changes. For example, when we used  $^1\text{H}$ -MRSI to compare NAA levels in patients who were first-episode at presentation and chronic, neuroleptically naive schizophrenics, we found similar alterations in this glutamatergic marker. In both patient groups, the localization patterns (hippocampus and prefrontal cortex) and the magnitude of NAA decreases were the same, suggesting that neuronal integrity was similar in acutely and chronically ill patients. We also found no support for the idea that

**Figure 3. Regional NAA/CREAT Signals in Patients With Schizophrenia and in Normal Controls<sup>a</sup>**

<sup>a</sup>From reference 20, with permission.

\*Statistically significant differences.

chronic, untreated psychosis led to neurodegeneration. Using <sup>1</sup>H-MRSI to detect choline signals associated with the proliferation of glial cell membranes during reactive gliosis, we saw no evidence of increased choline signals in any of our patient populations, suggesting that active degeneration of brain tissue is not taking place. We have also failed to detect significant neuronal loss using computerized tomography to study cerebral ventricular size in schizophrenic patients over a period of 7–10 years,<sup>33</sup> a result replicated by Andreasen and coworkers.<sup>34</sup> In addition to anatomical arguments against neurodegeneration, functional data also show that cognitive function (i.e., memory) does not decrease over time, despite clinical deterioration.<sup>35</sup> Together, these studies would seem to indicate that, while glutamate function may be altered in schizophrenia, it does not contribute to an excitotoxic/neurodegenerative process.

### GABA

GABA is the principal inhibitory neurotransmitter in the brain and the amino acid neurotransmitter of small cortical neurons. Like glutamate, the most compelling argument for the involvement of GABA in schizophrenia is that cortical malfunction appears to be a hallmark of the disorder. The robust interactions between GABA, dopamine, and glutamate in animal models, for example, implicate GABA as well as the other neurotransmitters. GABA-mimetic agents can also be psychotogenic, and their psychotogenic effects probably resemble schizophrenia more closely than the effects of NMDA antagonists. Finally, results from Benes and coworkers have described an increase in GABA<sub>A</sub> receptor density in postmortem tissue from patients with schizophrenia, consistent with a GABAergic deficit.<sup>36,37</sup>

While more research is clearly needed, the greatest drawback with GABA hypotheses is that drugs working

directly on these systems are not very impressive therapeutically in patients with schizophrenia. It remains to be seen if the newest atypical neuroleptics will have a pharmacologic profile consistent with an etiologic role for amino acid neurotransmitters.

### THE NEURODEVELOPMENTAL HYPOTHESIS

An abnormality of brain development has become increasingly popular as an underlying biological factor in schizophrenia.<sup>38</sup> While a sizable database favoring abnormal brain development as a pathologic mechanism has been assembled, the available data provide inconclusive evidence of developmental neuropathology in schizophrenia. Probably the most compelling evidence that patients with schizophrenia are abnormal during childhood comes from two epidemiologic studies of British birth cohorts.<sup>16,39</sup> These prospective studies found neuromotor and social deficits present during infancy and childhood that were associated with the diagnosis of schizophrenia in adult life. These studies clearly demonstrate that patients with schizophrenia are abnormal from a very young age, yet fail to decisively implicate abnormal brain development as the etiologic factor.

The neuroanatomical data, derived primarily from neuroimaging studies, are provocative but still inconclusive. Imaging studies supporting the neurodevelopmental hypothesis have demonstrated the presence of morphometric abnormalities at the time of diagnosis, such as enlarged cerebrospinal fluid spaces and reductions in cortical volume, that correlate with premorbid functioning.<sup>40,41</sup> Cytoarchitectural abnormalities found in the postmortem brain of schizophrenia patients are currently the strongest evidence supporting the neurodevelopmental hypothesis. The most important of these are defects in

laminar organization of the entorhinal cortex.<sup>19,21</sup> Neurons normally found in the superficial layers of the entorhinal cortex were displaced to ectopic locations in deeper layers, suggesting a failure to migrate from the subplate zone during the second or third trimester of gestation. This failure of neuronal migration could ultimately lead to altered connectivity between the entorhinal cortex and hippocampus. These results, however, have not been independently replicated. Moreover, the regional anatomy of the entorhinal cortex is also highly variable in normal subjects and, in fact, can resemble the abnormalities described, for example, in schizophrenia.<sup>21</sup> In order to validate the earlier findings, it is critical that all future studies compare the identical cytoarchitectonic areas of the entorhinal cortex in patients and controls.

Studies by Akbarian and colleagues<sup>42,43</sup> also examined the cytoarchitecture of brains from schizophrenic patients using a neurohistochemical technique and found a defect of neuronal migration similar to that reported by Jakob and Beckmann<sup>21</sup> and Arnold and colleagues.<sup>19</sup> Histochemical analysis of cortical neurons expressing the enzyme nicotinamide-adenine dinucleotide phosphate-diaphorase (NADPH-d) revealed a distorted distribution of NADPH-d neurons in the dorsolateral prefrontal cortex and lateral temporal lobe. The increased presence of NADPH-d positive neurons in the deeper layers of these cortical regions was attributed to a disturbance of the normal inside-out migration of these neurons during development. However, a more recent report by this same group only partially replicated the original findings.<sup>44</sup> While the initial study found prefrontal derangement of NADPH-d positive neurons in 5 of 6 patients, the most recent described a similar defect in only 7 of 20 patients, including the original 6 patients. Therefore, 5 of the 7 subjects with cytoarchitectural anomalies in this second report are actually from the initial study population, meaning that only a small minority of the new sample (2 of 14 patients) expressed the defect. Clearly, this finding will need to be independently replicated in a larger sample before it can be considered truly convincing evidence of a cytoarchitectural disturbance in schizophrenia.

Another challenge that must be met by the neurodevelopmental hypothesis is explaining how the disease remains quiescent for 20 years and then suddenly manifests. A complete answer to this question awaits further research. However, existing data are consistent with the hypothesis that subtle abnormalities of intracortical neural systems that use GABA and glutamate as their principal neurotransmitters may not become functionally apparent until the time of life when these systems should be fully operative. For example, the Wisconsin Card Sorting Task, an excellent predictor of overall disability and long-term outcome in schizophrenic patients, is a task in which children do not reach optimal performance until the second decade of life, following the maturation of the late-

developing intracortical cognitive neurosystems. The observation that schizophrenics have difficulty with this task may indicate that these late-maturing neurosystems are disrupted. Similarly, abnormalities of the prefrontal cortex, an excellent example of a brain region that does not reach functional maturity until early adulthood, may remain silent until cortical maturation is complete.

Independent replication of the cytoarchitectural anomalies described above, or of other, perhaps molecular, evidence of brain maldevelopment, utilizing strict experimental and anatomical controls, will determine the strength of the case that can be built for the neurodevelopmental hypothesis. The finding of changes that could only be explained by disturbances in brain development would provide incontrovertible evidence in favor of the neurodevelopmental hypothesis.

### Novel Animal Models

On the basic research front, new theories of the pathogenesis of schizophrenia, especially neurodevelopmental theories, promise biologically plausible animal models that more accurately recreate the natural history and behavioral pathology of the illness. The traditional "dopamine-in/dopamine-out" animal models, used to develop and test most of the currently available drugs for the treatment of schizophrenia, were based directly on manipulations of the dopamine systems. Not surprisingly, the drugs that resulted from this research strategy have antidopaminergic effects.

Newer models, however, based on the neurodevelopmental hypothesis, focus on experimental disruption of cortical development. For example, our laboratory has developed a rodent model based on excitotoxic injury of the hippocampus that interrupts connections between the limbic system and cortex during the vulnerable neonatal period. This model appears to mimic some of the key neurobiological characteristics of schizophrenia.<sup>45-47</sup> In particular, the animals with the hippocampal lesion do not display the schizophrenia-like behavioral, neurochemical, or molecular changes until they reach sexual maturity.<sup>45</sup> In addition, lesioned animals respond preferentially to atypical neuroleptics such as clozapine compared with the traditional dopamine antagonist haloperidol<sup>46</sup> and also display enhanced sensitivity to glutamate antagonists.<sup>47</sup> Future research using animal models that are not based on fundamental perturbations of dopamine should allow us a better understanding of the underlying pathophysiology of schizophrenia and the pharmacologic actions of novel antipsychotic drugs.

*Drug names:* clozapine (Clozaril), haloperidol (Haldol and others).

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