CHAPTER 12. SCHIZOPHRENIA

12.4 SCHIZOPHRENIA: NEUROBIOLOGY

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Schizophrenia is a chronic mental illness affecting approximately 1 percent of the population. Beginning in early adulthood, schizophrenia typically causes a dramatic, lifelong impairment in social and occupational functioning. From a public health standpoint, the costs of treatment and lost productivity make this illness one of the most expensive disorders in medicine. Despite the tremendous economic and emotional costs, research on schizophrenia lags far behind that on other major medical disorders. A primary impediment to developing more effective treatment is the limited understanding of the etiology and neurobiology of this disorder. New technologies, such as neuroimaging and molecular genetics, are removing the obstacles that once blocked major progress in the field. Although the stigma associated with the illness has not yet been eliminated, these new techniques have markedly altered the conception of the nature of schizophrenia.

One of the most rapidly changing fields is genetics. Family, twin, and adoption studies have clearly shown that genes play a prominent role in the development of schizophrenia. Estimates of heritability typically range from 50 to 85 percent. Initial attempts to isolate major genes using linkage studies were unsuccessful, but more recent approaches using increasingly sophisticated methods have uncovered several chromosomal regions that may harbor genes of minor effect. It seems likely that schizophrenia is the result of the interaction of many genes, some of which also interact with environmental factors. Investigations of environmental factors have looked at the role of stress, viruses, obstetrical complications, and in utero insults, among others. None of these have been definitively shown to be causative. It is possible that different combinations of genetic and environmental factors affect specific neurobiological systems, leading to a final common pathway of neural dysfunction.

Several neurobiological abnormalities have been found to have major implications for understanding the

pathophysiology of schizophrenia. The first are structural brain abnormalities. Initially seen decades ago using pneumoencephalography, structural changes have been more clearly delineated using computerized tomography (CT) and magnetic resonance imaging (MRI). The most commonly reported alterations include enlarged lateral ventricles, enlarged third ventricle, and reduced volume of a number of structures, including hippocampus, amygdala, and frontal and temporal cortices. These abnormalities may predate the onset of illness. Second, functional cortical deficits have been seen with a variety of techniques, such as neuroimaging and neuropsychological testing. Prefrontal and temporal lobe dysfunction is most prominent, and is possibly related to structural abnormalities. Third, neuropathological studies have consistently failed to find any evidence of gliosis to account for the structural deficits. If anything, they tend to find subtle cytoarchitectural alterations. The recurring theme of this research suggests some type of failure in neuronal migration, orientation, or connectivity. Finally, several neurotransmitter systems appear to play a role, particularly in the expression of positive as well as negative psychotic symptoms. Evidence for alterations in the dopamine system is the most compelling. Other neurotransmitters have also been implicated, including glutamate, serotonin, and γ-aminobutyric acid (GABA).

Neurochemical, structural, and functional imaging abnormalities can be understood in the context of the neural circuits involved and models of the illness. Cortico-striato-thalamic, limbic, and dopamine systems all appear to play a role. These three interconnected pathways mediate different aspects of higher-level information processing, such as judgment, memory, planning, and motivation. Their involvement could arise in several ways. One model suggests that neurodevelopmental abnormalities occur in utero. The clinical manifestations of schizophrenia appear only after brain development is largely completed, in late adolescence. Although this hypothesis has come to dominate thinking about schizophrenia, the neurodevelopmental model has several weaknesses.

ROLE OF GENES AND ENVIRONMENT

Genetic Factors Family, twin, and adoption studies indicate that there is a major heritable component to schizophrenia. Whereas the incidence in the normal population is approximately 0.5 to 1 percent, the lifetime risk in first-degree relatives is roughly 10 percent, indicating that the risk to first-degree relatives is 10 times that of the general population. This strongly implicates a familial factor in the etiology of the illness. Twin and adoption studies have shown that this is mostly, if not entirely, due to genetic factors. For example, the concordance rate in monozygotic twins is approximately 50 percent, as compared to 10 to 14 percent for dizygotic twins, suggesting that heritability may be as high as 80 percent. Of seven adoption studies, all found an increased incidence of schizophrenia in biological relatives, but not in adoptive relatives. This data convincingly demonstrates that genetic factors rather than shared, familial environmental factors are at work.

Although such epidemiological data implicate a major heritable component, the genetic architecture appears complex. Early attempts at modeling genetic transmission in families (using segregation analysis) suggested that heritability could not be explained by a single, dominant gene. In the early 1990s, increasingly sophisticated modeling indicated that at least several genes were involved, each with

incomplete penetrance. One very real possibility is that there are many genes of minor effect. Such genes are difficult to detect using traditional linkage approaches. A triggering role for the environment in those with a genetic predisposition has also been hypothesized. While genetic modeling has been heuristically useful, the lack of a clear genetic mechanism complicates attempts to find the causative genes.

Early linkage studies were based on traditional assumptions that a single dominant gene produced the illness. These were, in general, unsuccessful. The first published study to use restriction fragment length polymorphisms (RFLP) reported linkage between two markers on the long arm of chromosome 5 (5q11-13) and schizophrenia. Subsequently, a number of other groups using separate cohorts were unable to replicate this, and several were able to clearly reject linkage to loci from 5q. While this failure dampened enthusiasm for genetic studies of schizophrenia, the relentless advances in statistical genetics and the molecular biology of the human genome have provided powerful new tools for detecting genes of minor effect. For example, some of the problems with specifying the unknown parameters needed for linkage analysis can be circumvented by using nonparametric approaches. These approaches use large collections of sibling pairs, both affected with the illness. As investigators have begun to use such tools, positive linkage reports for schizophrenia susceptibility genes of minor effect have been reported. Recent examples of putative schizophrenia susceptibility loci yielding some evidence of confirmation include loci on chromosomes 6, 8, and 22.

Despite real advances, several statistical issues continue to complicate interpretation of linkage studies. First, ambiguities persist about what diagnoses should be included. Family and adoption studies have suggested that diagnoses such as schizoaffective disorder, schizotypal personality disorder, and atypical psychosis are genetically related. To hedge their bets, investigators looking for linkage typically test several definitions of “schizophrenia spectrum,” ranging from narrow to very broad inclusion criteria. This means that more family members are included in the analysis as diagnostic criteria broaden. Second, the issue of which genetic model to use continues to plague parametric approaches. Typically, linkage studies include dominant, recessive, and mixed models. Here again, investigators hedge their bets by testing three or four genetic models. Since both problems lead to multiple testing, correction for multiple comparisons is indicated. Unfortunately, it is not entirely clear how to correct for this multiple testing. Currently, the commonly accepted significance level (*p* values) for initial linkage reports is ~10_{-4} to 10_{-5} or a logarithm of the odds (LOD) score of 3.3 and 0.01 for confirmation. Several groups have published putative replications of linkage findings based on these statistical criteria.

The first linkage study with some independent confirmation came from a study of a large Irish cohort. Using microsatellite markers and 186 multiplex schizophrenia families, evidence was found for linkage to the short arm of chromosome 6 (6p22). However, when adjusting for multiple comparisons, a genome-wide significance was estimated at .05 to .08 percent. When the original cohort was extended to 265 pedigrees, an LOD score of 3.51 was obtained, again using a moderately broad definition of illness. The LOD score was highest with a model of intermediate penetrance; of note, only 15 to 30 percent of pedigrees were linked. Supportive evidence for linkage to 6p22 was found in three independent studies. Interestingly, the three replications were different from the original in several ways; one used a recessive

model and a narrow definition. In contrast to the original findings, a dominant model and broad disease definition yielded an LOD score of 0.06. A second replication study found suggestive linkage at a marker very close to the one in the original report. Not unexpectedly, a number of studies have failed to replicate the D6p22 linkage. These results illustrate some of the complexities of linkage studies of schizophrenia, but also provide some hope that these methods will uncover the genes involved in schizophrenia.

In addition to 6p22-24, at least two other regions have yielded evidence of linkage to schizophrenia. Ann Pulver and colleagues first described evidence for suggestive linkage to chromosome 8 at 8p22-p21 using 57 multiplex families. Soon after, another group, using a very broad definition of illness, reported confirmatory evidence for linkage using the Irish cohort; again, only 10 to 25 percent appeared to be affected by this putative susceptibility gene. A second attempt at replication by a multicenter collaborative group also found support for linkage. Suggestive evidence for a third potential vulnerability locus was reported for chromosome 22 at q12-q13.1.

Although the evidence for susceptibility loci in these reports does not overlap completely, the differences in location are not large. In other heritable complex diseases, for example, susceptibility genes have been cloned that are 20 centimorgans (about 20 million base pairs) away from the sites initially linked to the illness. As with 6p22-24, the strength of evidence for linkage to both 8p22-p21 and 22q12-q13.1 depends in part on what is acceptable as a significant replication. This in turn is related to how multiple tests are corrected for using a variety of phenotypes and model parameters. It is possible that there are schizophrenia susceptibility genes in a roughly 10 to 20 cM area in these regions that may each affect a small percentage of families. Several other regions have received attention but the evidence is less compelling. These regions include, at present, 5q, 6q, 9p, 18p, and 22q.

Using the candidate gene approach, weak support for involvement of the dopamine type 3 (D_3) receptor gene has emerged. In 1992, an excess of homozygosity was noted in schizophrenia patients compared to controls for a polymorphism in the first exon of the D_3 receptor gene. A few subsequent studies have supported a modest association between schizophrenia and homozygosity of the Ser-9-Gly polymorphism, but a large number of other studies failed to replicate this association. Linkage studies with D_3 receptor gene polymorphisms have not found significant LOD scores. As more functional variants in candidate genes are discovered, focused association studies of these genes will become increasingly common.

It is crucial to determine exactly what is inherited. One possibility is that genes determine susceptibility to certain environmental factors. Another possibility is that specific neurobiological abnormalities are produced by specific genes. Family studies have shown that relatives have an increased incidence of several neurobiological traits associated with schizophrenia. These include structural brain abnormalities, changes in evoked potentials, eye-tracking dysfunction, negative symptoms, and subtle cognitive deficts. These parameters could be more basic phenotypes that are closer to the molecular manifestations of the genes that cause schizophrenia. If so, they may improve the ability to detect these genes.

Environmental Factors Family-based epidemiological studies clearly demonstrate that environmental factors play a role in the pathophysiology of schizophrenia. The contributions of environmental factors have been estimated to be as much as 30 to 50 percent. Genetic modeling indicates that genes could set the threshold for liability to environmental factors. It is sobering to realize that environment can play a crucial role even in disorders that appear to be autosomal dominant. For example, phenylketonuria is an autosomal-dominant disorder that causes mental retardation. The illness is expressed, however, only if individuals with the abnormal gene ingest phenylalanine. Without this critical environmental exposure, the illness does not develop. Environmental factors hypothesized to play a role in schizophrenia range from problems with maternal bonding and early rearing to poverty, immigration status, stress, and viruses. The neurodevelopmental hypothesis has shifted the research focus somewhat from psychosocial variables to those that affect brain development. Several specific insults have been implicated, including pregnancy and birth complications, in utero viral infections (such as influenza), season of birth, and prenatal starvation.

Research into pregnancy, obstetric, and neonatal complications has had a particularly significant impact on the field. These complications include events such as prolonged labor, prematurity, preeclampsia, toxemia, fetal distress, and hypoxia. The majority of studies examining the incidence of such complications find increases in patients with schizophrenia. Positive studies include those that compare patients with matched controls, with their own well siblings, and even with a monozygotic twin discordant for schizophrenia. On the other hand, several impressive negative reports, including prospective, epidemiological surveys have failed to find a significant increase in such complications. However, these studies have been criticized on methodological grounds, thereby leaving the issue in doubt. Some authors have suggested that perinatal complications may increase risk only in persons with a genetic predisposition whereas others assert just the opposite. Although these conflicting findings make definite conclusions tentative, the bulk of the data suggests that perinatal complications are increased somewhat in patients with schizophrenia.

One possibility for how such complications lead to schizophrenia is that they produce some type of brain damage. The hippocampus, for example, is particularly susceptible to perinatal hypoxia and this limbic structure is thought to play an important role in schizophrenia. A number of studies have found that patients with a history of obstetric complications have increased likelihood of structural brain abnormalities, such as enlarged ventricles. A similar relationship has been seen in nonschizophrenic controls with a history of obstetric complications. However, many studies have failed to find any relationship between structural abnormalities and obstetric complications. Some authors have suggested that only nongenetic forms of the illness (sporadic cases) are more likely to have structural problems and obstetric complications, but data on this are very mixed. More problematic, obstetric complications are thought to mediate increased risk by transient hypoxia but hypoxia typically produces gliosis, a finding notably absent from the postmortem literature on schizophrenia. An alternative explanation is that obstetric complications are themselves secondary to abnormal fetal brain development. In any event, if obstetric complications increase the risk of schizophrenia, they are likely to be a minor factor; most persons with these complications do not develop schizophrenia and most patients with schizophrenia do not have an obvious history of obstetric complications.

A second risk factor that has been extensively studied is season of birth. There appears to be an increased incidence of schizophrenia associated with winter and spring birth dates. This finding is controversial, and has been attributed by detractors to a statistical artifact. If there is such a relationship, it could implicate an infectious process, such as a virus; viral infections are more common during winter months. Viral hypotheses have taken several forms, and candidates include slow viruses, retroviruses, or virally activated autoimmune reactions. In a related vein, several large-scale epidemiological studies have reported that the frequency of schizophrenia is increased following exposure to influenza during the second trimester. The effect is slight, however, and some studies have not observed this relationship. Another intriguing risk factor is starvation or poor nutrition. In studies of the effects of starvation during World War II in Holland, researchers found that starvation at the time of conception and in the first trimester increased the risk of developing schizophrenia by a factor of 2. Other factors recently reported to increase the risk of schizophrenia include Rh incompatibility and low intelligence quotient (I.Q.).

At this point, no single major factor has been unambiguously identified as an environmental cause of schizophrenia, and it is likely that none exists. As with genetic loci, environmental effects probably consist of a variety of factors, each having a minor effect at best. These will be difficult to detect, as will their hypothesized interaction with genes of minor effect, without large-scale studies.

STRUCTURAL AND FUNCTIONAL NEUROIMAGING

Neuroimaging studies of schizophrenia have demonstrated alterations in both structural and functional measures. Structural abnormalities include increased volume of the third and lateral ventricles, sulcal widening, and reduced volume of gray matter regions. Functional abnormalities include alterations in blood flow and measures of chemical moieties using MRI spectroscopy. Neuroimaging has also been used to assay receptor density and dynamic parameters related to dopamine release. Neurochemical studies are discussed separately in sections on specific neurotransmitters.

Neuroimaging has had a major impact on the conceptualization of schizophrenia. The notion that patients with schizophrenia have an actual deficit in the volume of brain tissue clearly established that this was a brain disease rather than a purely psychological or biochemical disorder. Functional neuroimaging has implicated the prefrontal and temporal lobes in particular, and has begun to relate activity in these regions to the clinical manifestation of schizophrenia. As critical as these findings have been, important controversies remain.

Structural Abnormalities One of the most widely replicated neurobiological findings in schizophrenia research is that of altered volume of cerebral structures. Increased size of the cerebral ventricles and reduced brain volume were observed early in the twentieth century using pneumoencephalography and postmortem material. These early findings, however, had little enduring impact on the field. The advent of CT technology renewed interest in cerebral volumetric parameters. The earliest CT studies found enlargement of the lateral and third ventricles and cortical sulci. Although these findings were initially viewed with skepticism, over 100 subsequent studies have been published with lateral ventricular enlargement reported in 75 percent, third ventricular enlargement in 83 percent, and cortical changes in

67 percent. Concerns that ventricular enlargement could be secondary to factors such as antipsychotic medications, institutionalization, and diet have generally been ruled out. Furthermore, studies using MRI, with its markedly enhanced resolution, have confirmed the presence of lateral and third ventricular enlargement and provided estimates of tissue loss to be roughly 3 to 10 percent.

The finding of ventricular enlargement dramatically shifted the focus of research on schizophrenia. Subsequently, several critical questions have dominated this landscape. First, is ventricular enlargement caused by focal areas of tissue loss or a more generalized process? Second, do the structural abnormalities predate the onset of the illness, implicating a neurodevelopmental process, or do they arise concomitantly with the illness, suggesting a neurodegenerative process? Third, are all patients affected or only a subgroup? Finally, what are the functional implications of these abnormalities?

To localize brain abnormalities, researchers have looked at a variety of measures, including cortical sulcal enlargement, ventricular enlargement, and quantitative measures of individual brain structures. Regarding cortical sulcal enlargement the data are split, with some reporting sulcal enlargement in the frontal and temporal lobes whereas others have found more diffuse enlargement. More specific measures of cortical volume typically show reductions of temporal and, less consistently, frontal lobe volume. These reductions involve gray rather than white matter, although some studies have found reductions in white matter as well. Regional volumetric studies of specific brain structures have generally focused on the temporal lobes. Bilateral volume reductions in amygdala-hippocampus, parahippocampal gyrus, entorhinal cortex, and superior temporal gyrus have been reported. In the ventricular system, increased volume in the temporal poles of the lateral ventricles has been found most often; increased volume of the frontal horns and third ventricle is also commonly found. In quantitative studies of subcortical regions, findings have been mixed. Some researchers find no changes in areas such as caudate, putamen, nucleus accumbens, and external segment of the globus pallidus; others have reported increased striatal volume and reduced globus pallidus (internal segment) volume. Increased striatal volume is thought to be an effect of treatment with antipsychotic medications. Reduced volume of the thalamus has also been observed.

The notion that the temporal and frontal lobes may play a particularly important role in schizophrenia has been supported by findings from other areas. For example, neurological damage to the temporal lobes sometimes produces positive psychotic symptoms, such as hallucinations, while damage to the frontal lobes is associated with negative symptoms such as apathy, social withdrawal, and blunted affect. On neuropsychological testing, patients with schizophrenia typically show impaired frontal and temporal lobe function. More recently, magnetic resonance spectroscopy has been used to examine these regions. This new technology can measure in vivo concentrations of a variety of neurochemical moieties. These include *N*-acetyl aspartate (NAA), an intraneuronal amino acid sensitive to mitochondrial energy metabolism and to pathological processes affecting neuronal integrity, choline-containing compounds, creatine plus phosphocreatine, glutamate, glutamine, and high-energy phosphate-containing compounds. Several intriguing findings have emerged. First, specific reductions of NAA have been observed in the dorsolateral prefrontal cortex and hippocampal area, probably reflecting neuronal pathology in these locations. Other areas are, for the most part, unaffected. Second, an imbalance between phosphomonoesters and phosphodiesters has been described in the frontal cortex. These studies,

combined with volumetric data, lend support to the theory that there may be selective deficits in frontal and temporal regions.

Attempts to pinpoint when volumetric alterations occur have led to studies of patients at the onset of their illness. This issue is crucial to understanding what neurobiological processes could possibly account for structural abnormalities. In general, first-break studies have found the same alterations seen in prior studies of patients with chronic schizophrenia. These results are supported by the lack of relation between volumetric alterations and duration of illness or age of onset seen in studies of such patients. If an active process produced tissue loss, the loss would be correlated with illness duration, which it is not in most studies. On the other hand, cognitive deficits associated with schizophrenia do not progress but probably develop very early in the illness. Although portions of these deficits may be present even in childhood, a significant component probably develops sometime around the onset of the illness. It is not inconceivable that structural abnormalities could develop at the same time. Such changes would not necessarily be detected by first-break studies. Another approach has been to scan first-break patients when they initially present for treatment and then again several years later. The results have been mixed: some find no changes whereas others have suggested that a subgroup of patients do show slight, but progressive tissue loss. The latter approach has been criticized on methodological grounds and certainly more studies are needed. At present, it seems fairly certain that structural abnormalities are present from very early on in the illness.

A third issue is whether structural alterations are present in all patients or only a subgroup. Several early studies had found associations between ventricular enlargement and a variety of clinical characteristics, including poor premorbid adjustment, age of onset, cognitive impairment, negative symptoms, poor response to antipsychotic medications, and greater incidence of tardive dyskinesia. Such observations have led to suggestions that there are two forms of schizophrenia, one involving a hyperdopaminergic state and the other involving structural abnormalities. Since then, many CT and MRI studies have examined this issue but have generally failed to confirm this schema. Structural abnormalities do appear to be correlated to some degree with cognitive impairment and negative symptoms, but these correlations are not particularly robust. Another approach to subtyping has been to look at the distribution of these deficits. In a meta-analysis of studies that have used CT scans to evaluate ventricular enlargement, the lack of a bimodal distribution in over 1000 patients suggests that a clear subgroup with these abnormalities does not exist.

An elegant attempt to assess the frequency of structural abnormalities was provided by a study of discordant monozygotic twin pairs. Unaffected monozygotic twins serve as an ideal control for assessing illness-related changes. In an MRI study of 15 such pairs, the ill twin had more pronounced deficits for most structural measures in over 85 percent of cases. These findings are similar to those of a prior twin study using CT scans. The data suggest that volumetric abnormalities in schizophrenia are very common, if not ubiquitous; detecting the abnormality may depend on having a perfectly matched genetic control (Fig. 12.4-1) because patients with normal ventricular volume were often seen to have significantly larger ventricles than their unaffected twin. However, when this MRI study of twins was expanded to 27 discordant pairs, lateral ventricular enlargement was only seen in about 63 percent of the affected twins relative to the unaffected twins. This is only somewhat higher than 50 percent, which is

what would be expected by chance. In this expanded sample, it appears that ventricular enlargement may not be universal. In contrast, hippocampal measures continued to predict the affected twin in roughly 80 percent of cases, which is significantly higher than the 50 percent chance level; this suggests that hippocampal pathology is common. Although the exact percent of patients having structural abnormalities is not known, it is probably fairly high. An alternative view is that structural abnormalities represent a quantitative trait that is commonly associated with schizophrenia but neither necessary nor sufficient to produce the illness.

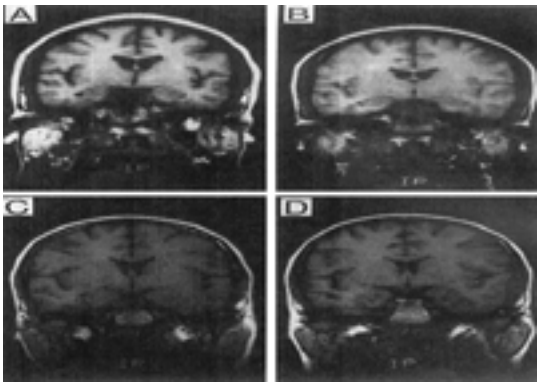


FIGURE 12.4-1 MRI scans (coronal sections) of two sets of discordant monozygotic twins (**A** and **B** = set 1; **C** and **D** = set 2). For each pair, one has schizophrenia (**A** and **C**) while the other does not (**B** and **D**). For both pairs, the affected twin has larger ventricles than the unaffected twin, even though ventricular size appears to be within the normal range for the affected twin (C). (Courtesy of D. Weinberger and E. F. Torrey.)

In summary, structural abnormalities, such as enlarged ventricles and reduced cortical volume, are a prominent feature of schizophrenia. It is unclear whether cortical involvement is multifocal or diffuse. Temporal and frontal lobe regions are certainly involved. These abnormalities are present very early in the illness. It is too early to say, however, whether they are present from birth or develop at a later stage. Structural abnormalities may be present in a majority of patients, although the exact percentage is unknown. The prevalence is most apparent when compared to ideally matched genetic controls. Structural abnormalities are correlated to some degree with clinical aspects of the illness, such as cognitive deficits. A key issue remains unresolved: what neurobiological processes account for these enigmatic changes?

Functional Neuroimaging Functional neuroimaging refers to a group of methods that look at changes in regional neural activity by measuring regional cerebral blood flow (rCBF) or glucose utilization. These two parameters can be measured with several techniques, including positron emission tomography (PET),* (SPECT), and more recently functional MRI (fMRI), each having its own particular advantages and disadvantages. These techniques have been used to explore brain regions that may be dysfunctional in schizophrenia. Several designs have been employed: (1) patients and controls are compared at rest; (2) they are compared during cognitive testing that normally increases activity in a particular brain region; and (3) brain activity is correlated with psychiatric symptoms, either cross-sectionally among patients or within a patient over time. The most consistent finding is reduced activation of the prefrontal cortex (hypofrontality), but other regions, such as the temporal lobes, have also been implicated. Also, correlations have been found between specific symptom clusters and regional activity in both frontal and temporal areas (Fig. 12.4-2).

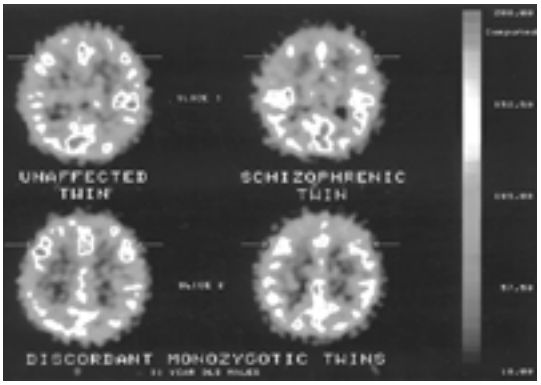


FIGURE 12.4-2 PET scans using H_2O_{15} of two monozygotic twins, one with (right) and one without (left) schizophrenia. Top and bottom scans show two levels through the dorsolateral prefrontal cortex. At the time of scanning, subjects are performing a cognitive task that typically requires prefrontal cortical function. The affected twin blood flow to the dorsolateral prefrontal cortex is markedly reduced compared to the unaffected twin. (Courtesy of R. Berman and D. Weinberger.)

Frontal lobe function has been studied most intensively. Initially reported in 1974, the finding of reduced frontal blood flow has been controversial. Many studies, particularly those looking at the resting state, have not found evidence of hypofrontality. Such studies have been criticized, however, because the resting state is an uncontrolled feature and may introduce unnecessary variability. Using cognitive tasks that appear to require prefrontal activation in controls, a number of studies have consistently found that patients with schizophrenia fail to increase blood flow to this region. Although many resting studies have reported hypofrontality, most, if not all, studies using activation tasks have found hypofrontality; this suggests that the use of activation tasks can increase the sensitivity of these procedures to detecting abnormalities by assessing function of regions involved in the illness (Fig. 12.4-2).

The finding of hypofrontality in schizophrenia has often been interpreted as an artifact of poor performance, motivation, clinical state, medications, or other factors. However, studies have not shown that these factors account for differences between patients and controls. For example, poor performance on working memory tasks is not necessarily associated with reduced prefrontal blood flow. Patients with Huntington's disease and groups with low I.Q. who do equally poorly on prefrontal cognitive tasks, are able to activate the dorsolateral prefrontal cortex. Interestingly, hypofrontality appears to be correlated with several structural and neurochemical indices. Prefrontal activation is highly correlated with homovanillic acid (HVA) concentrations in cerebrospinal fluid, possibly reflecting prefrontal dopamine activity. Hypofrontality has also been correlated with hippocampal volume in one study of discordant monozygotic twins, suggesting a dysfunctional circuit. Finally, preliminary reports suggest that reduced prefrontal NAA concentrations, markers of neuronal integrity, are correlated with reduced frontal activation. These data imply that hypofrontality could result from a process that affects neuronal viability in both frontal and hippocampal regions and that these have downstream effects on the regulation of prefrontal dopamine.

The temporal lobe has also been examined with functional neuroimaging techniques. Both elevated and reduced blood flow has been reported. The most common finding is an association between resting blood flow and positive psychotic symptoms. For example, one report found a correlation between

increased psychopathology and blood flow to the left parahippocampal gyrus; a second found a similar correlation between positive symptoms and left temporal lobe blood flow. More specific correlations have been seen for auditory hallucinations and activation of Broca's area and medial temporal regions. A potential criticism of this finding is that patients may have simply been responding to auditory hallucinations with their own vocalizations. Activation of Broca's area, in this case, would be expected and trivial. Research into the relation between symptom clusters and blood flow revealed that positive symptoms were associated with increased medial temporal flow, negative symptoms with decreased prefrontal (dorsolateral) blood flow, and disorganization with increased cingulate flow. This parcelation of symptoms with neuroanatomy suggests that separate but related neurophysiological processes may underlie specific types of symptoms. The few studies that examine several regions simultaneously tend to find changes in the coordinated activity between regions, particularly between prefrontal and temporal areas. Typically, increased activation in temporal areas is found in functional connectivity of the two regions.

One report on other brain regions found increased left globus pallidus activity at rest; others have reported both decreased and increased glucose utilization in the striatum (Fig. 12.4-3). Antipsychotic medications appear to increase striatal metabolism, suggesting that medications are an important confound. Reduced cingulate activation has also been described. As newer techniques that do not depend on radioactivity, such as fMRI, are more commonly used, further characterization of these and other brain regions can be expected.

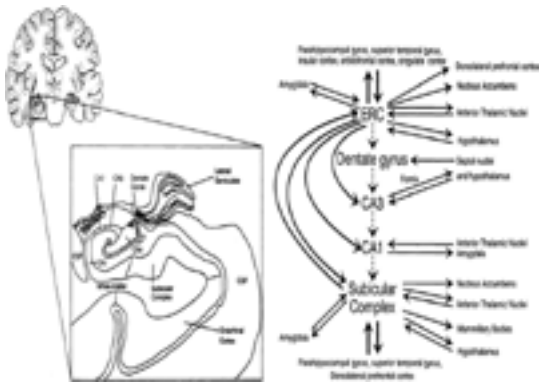


FIGURE 12.4-3 A, Schematic diagram of the mesial temporal lobe at the level of the body of the hippocampus and posterior entorhinal cortex, in coronal section. **B**, The illustrated connections of the coronal section are described in this table. (Drawn by Kyle Christensen.)

In summary, blood flow to several brain regions, including prefrontal and temporal areas, is altered in schizophrenia. These changes may be related to or may underlie positive and negative symptoms as well as some cognitive deficits. Regional abnormalities may also be related to each other, indicating a more global problem with the function of the larger systems or neural networks. Many questions remain. How closely are the changes in temporal and prefrontal activity associated with the clinical features of schizophrenia? Is the activation of other brain regions affected? Can functional brain imaging pinpoint which brain areas cause specific symptoms? What neurobiological processes account for differences in brain function? Correlations with structural abnormalities, dopamine metabolites, and regional NAA levels suggest that these variables could play a role.

NEUROPATHOLOGY

The neuropathological basis of schizophrenia remains obscure despite an increased number of techniques applied to the investigation of this subject. The future appears bright, however, as more laboratories across the world become engaged in this research. Regions that have become the focus of postmortem studies include temporal and limbic structures (hippocampus, amygdala, hypothalamus, nucleus accumbens, and cingulate cortex), and prefrontal and orbitofrontal cortices. Other paralimbic structures recently have been added to the neural network thought to be dysfunctional in schizophrenia, including the ventral tegmental area, substantia nigra, anterior thalamic nuclei, and entorhinal cortex. With this focused approach a number of intriguing findings have emerged; almost all still need independent replication, and the confounds of antemortem exposure to antipsychotic drugs must be considered when reviewing these studies.

Temporal Lobes

Mesial Structures Perhaps the one region that has received the greatest attention in postmortem schizophrenia research is the mesial temporal lobe, which contains the entorhinal cortex, amygdala, and hippocampal formation (Fig. 12.4-3). These structures have been examined in both morphological and neurochemical studies. The entorhinal cortex, which relays cortical input into the hippocampus and distributes output from the hippocampus to a diverse group of brain structures, has been carefully scrutinized. The laminar distribution of neurons in the superficial layers of the rostral entorhinal cortex has been reported to be abnormal and disorganized by several independent groups of investigators. One study in particular has suggested that the subtle changes in neuronal aggregation may be restricted to layers II and III. Taken together, these data suggest a mild disruption of normal cytoarchitectural features. Although it may not be impossible for this to occur later in life, the findings would strongly support the notion that abnormal neuronal migration may occur during brain development in patients with schizophrenia.

The finding that cytoarchitectural abnormalities are present in the entorhinal cortex have recently been contested by two carefully controlled, anatomically precise studies. Both studies failed to find the abnormal cytoarchitectural features described previously and suggested that earlier reports may have been confounded by incomplete matching of sections from normal controls and individuals with schizophrenia. The normal cytoarchitecture of the entorhinal cortex markedly changes along its rostrocaudal extent, making the issue of appropriate matching critical. However, the entorhinal cortex may not be entirely normal in schizophrenia; one study found a limited reduction in neuronal number and density. This is consistent with other reports of smaller volume, a reduction in the number of neurons, and volumetric measures using MRI.

Neurochemical elements that subserve the anatomic integrity of a given brain region have also been measured, as an indirect assessment of the cytoarchitecture. Microtubule-associated proteins (MAPs) are important elements of the neuronal cytoskeleton. One recent study found a marked loss of MAPS immunoreactivity in the subiculum and the entorhinal cortex in schizophrenia. This finding was interpreted as support for and evidence of cytoarchitectural abnormalities in this mesial temporal lobe.

However, given the qualitative nature of most immunostaining techniques, direct replication and additional investigations with more quantifiable strategies are needed.

Synaptophysin is a synaptic vesicle protein, and as such is widely distributed throughout the central nervous system. Levels of synaptophysin or its mRNA on both can be used as indices of synaptic density. Decreased synapsin I, but not synapsin IIb or synaptophysin, has been found in the hippocampus of patients with schizophrenia. A more recent report noted a reduction in synaptophysin messenger ribonuclei acid (mRNA) in CA4, CA3, subiculum, and the parahippocampal gyrus. There were no changes in synaptophysin in these regions, however, suggesting that the loss of synapses may occur at extra-hippocampal sites. Alternatively, local circuits within the hippocampus may be compromised but the ability to detect these changes is limited by the volume of extra-hippocampal input to this brain region. In any event, this finding is another element in the emerging picture of structural alterations in the mesial temporal lobe.

Hippocampus The hippocampus, the predominant structure within the mesial temporal lobe, also may have anatomic abnormalities. Postmortem studies of the hippocampus have proliferated since the mid-1980s. One group found a volume reduction in the whole hippocampal formation in schizophrenia. Others, however, have reported that decreased volume is restricted to the white matter of the left hippocampus, or in the volume of the CA4 subfield. A number of other postmortem studies have found subtle structural abnormalities in the hippocampal formation in schizophrenia, providing a relatively robust body of evidence implicating alterations of the hippocampal formation in schizophrenia.

Within the pyramidal cell layer of the hippocampus, the most recognizable microscopic feature is the orientation of pyramidal cells. While cellular disarray in the CA1-prosubiculum and CA1-CA2 interface has been observed by one group, at least three other groups were unable to replicate this finding. Decreased numbers of pyramidal cells in hippocampal subfields and reduced neuronal size (in left CA1 and CA2, and right CA3) have also been found. These are both consistent with prior MRI findings. Alteration in the density of staining of the mossy fibers in the hilus of the dentate gyrus, and several hippocampal subfields have been seen as well. However, this finding is surprising because cell loss in the adjacent entorhinal complex should lead to an increase in the staining density of the mossy fibers. Finally, decreased polysialic acid-neural cell adhesion molecule (PSA-NCAM) immunoreactivity has been reported in the CA4 subfield of the hippocampus in schizophrenia. PSA-NCAM, a cell adhesion molecule, is thought to be important in synaptic rearrangements in adulthood. Although no clear consensus has emerged on the nature of pathological change within the hippocampus proper, there is abundant evidence of structural abnormalities.

Amgydala The amygdala, located within the mesial temporal lobe, has major interconnections with the entorhinal cortex and hippocampus, as well as many other structures. The amygdala appears to have a smaller volume in schizophrenia patients; this finding is in accordance with postmortem reports.

Prefrontal Cortex Postmortem studies of the prefrontal cortex have been stimulated by the deficits observed with in vivo neuroimaging. One recent study found increased neuronal density in prefrontal

area 9; a change of similar magnitude was observed in occipital area 17 as well, suggesting a widespread pathological process. This finding was interpreted as representing a loss of neuropil throughout the cortex in schizophrenia without accompanying gliosis. Area 9 has also been shown to have a smaller average neuronal size and an increased density of smaller neurons, with unchanged glial size and density. The absence of gliosis again suggests that the pathological change in schizophrenia is probably not an active inflammatory process. Area 17, visual cortex, did not show any of these abnormalities, suggesting some anatomic specificity of this finding. In addition to smaller neuronal size, layer 3 pyramidal cells may have diminished dendritic spine density, which in part may explain the abnormalities in neuropil noted by others. Finally, area 46, prefrontal cortex adjacent to area 9, also has increased neuronal density in layers 2, 3, 4, and 6, and a thinning of layer 2. Taken together, these studies suggest a loss of neuropil in the prefrontal cortex, and abnormalities in the cellular constituency of this region.

A somewhat murky picture has emerged from studies of the distribution of neurons in the subcortical white matter underlying the prefrontal cortex. Such neurons are thought to represent a vestige of neuronal migration during early brain development. One group found an increased density of nicotinamide-adenine dinucleotide phosphate diaphorase-positive neurons in the deep white matter and a lower density in the superficial white matter underlying the superior and middle frontal gyri. This is consistent with a developmental arrest in the migration of cortical neurons from deeper white matter areas to superficial cortical layers. A second, similar study looked at MAP2-immunoreactive neuron distribution in the subcortical white matter underlying area 46 and the transition zone between areas 46 and 9 in the prefrontal region. Patients with schizophrenia had a greater density of MAP2-immunoreactive neurons in the superficial white matter compared to controls. In contrast to the first study, no differences are seen in deeper white matter. This was interpreted as either abnormal expression of MAP2, a defect in neuronal migration, a failure of programmed cell death, or a decrease in white matter volume in schizophrenia patients. Although these two studies looked at different neuronal subpopulations, the different findings are contradictory and must be interpreted with caution.

Orbitofrontal Cortex The orbitofrontal cortex has also come under scrutiny, at least in part because of interconnections with a variety of limbic system structures and the efficacy of leukotomy in the treatment of some clinical aspects of schizophrenia. In area 10, orbitofrontal cortex, a decrease in neuronal number, maximal in layers 4 and 5, and in cortical thickness has been observed in a small sample of schizophrenia subjects. A similar reduction in areas 4 (frontal), 24 (cingulate), and 17 (occipital), has also been seen, suggesting a pancortical process. A more recent study found a significant reduction in neuronal density in layer 6 of area 10, but also in layer 5 of area 24 (cingulate cortex) and layer 3 of area 4 (primary motor cortex). The meaning of changes in such disparate layers cannot be easily explained, especially in light of the findings in areas 9 and 17.

Neurochemical analyses also have been performed on the prefrontal cortex as an index of structural integrity. One group examined the concentrations of synaptic vesicle associated protein-25 (SNAP-25) a synaptosomal associated protein involved in neurotransmitter release. Using quantitative Western blots, they found an elevation in SNAP-25 concentrations in area 9, reductions in areas 10 and 20 (temporal cortex), and no change in area 17. Such findings could be due to either a change in synaptic density or to

an abnormality in neurotransmitter release; the former interpretation may account at least in part for the decreased neuropil in area 9.

Cingulate Cortex The anterior cingulate cortex (area 24) is part of the neural network subserving the cortical regulation of emotion and attention, both of which appear to be deficient in schizophrenia. In a series of postmortem studies, one group demonstrated an increase in vertical axon number in the cingulate cortex of schizophrenia patients. These researchers have also reported abnormalities in neuronal aggregation in layer 2 of area 24 and a decrease in the number of interneurons in layers 2-6 of this region. Others have seen an abnormality in the usual asymmetry of weight and surface area for the anterior cingulate cortex; independent replication of these findings will be important.

Other Regions Subcortical structures also may have an abnormal anatomy in schizophrenia. Consistent with MRI studies, the mediodorsal nucleus of the thalamus may have fewer neurons in schizophrenia patients in comparison to controls. Studies of the basal ganglia are somewhat limited. Whereas one study did not find any absolute volume differences in the striatum as a whole or individually in the caudate, putamen, or nucleus accumbens, a second group reported an increase in left striatal volume in schizophrenia patients. A third report on the ultrastructure of the caudate nucleus using electron microscopy found abnormalities in synaptic morphology and dystrophic and reactive changes in astrocytes. Regarding midbrain dopaminergic nuclei, decreased volume of the lateral substantia nigra, and a decrease in the average volume of the nerve cell bodies in the medial segment have been observed. Several other studies have found no significant brainstem pathology or relatively nonspecific findings. Clearly, more research needs to be devoted to the brainstem, given the importance of ascending catecholamine and serotonin systems in regulating the activity of forebrain structures, and the clinical data implicating these neurochemical systems in schizophrenia.

Gliosis Of all these subtle yet potentially important cytoarchitectural findings, one of the most critical observations is the apparent absence of gliosis. The importance of this stems from theoretical implication that reduced volume of brain regions and other abnormalities are not the result of an active pathological process: instead, they are likely to be secondary to very early developmental processes. The issue of whether gliosis is present has been addressed by many postmortem studies over the past century. Of these, at least a dozen recent studies have used methodologically superior quantitative techniques. While several have noted increased gliosis, the large majority has found no differences between brains from patients with schizophrenia and those from normal controls. These include studies using several different techniques for counting glial cell number, such as the Holzer stain, Nissl stain, and immunoreactivity for glial fibrillary acidic protein. Some methodological questions about the ability of some techniques to detect the effects of chronic gliosis persist; it seems unlikely, however, that clinically relevant gliosis would be obscured.

The wide variety of potentially important findings must be approached with a healthy skepticism. Several common problems plague almost all postmortem volumetric and cell counting studies in schizophrenia. First, standard stereological techniques, using serial sections at regular intervals through the rostrocaudal extent of the mesial temporal lobe, are infrequently applied. Fortunately, more recent studies are employing stereology with greater frequency. Moreover, rarely, if ever, is the time of fixation

carefully controlled, so that there is a wide variation within and across studies. Tissue shrinkage, which affects tissue volume and cell density, and maybe quality of cell staining, varies with the duration of fixation. Nevertheless, postmortem studies point to subtle volume reductions in the hippocampal formation in schizophrenia. The precise neuropathological changes that underlie this volume reduction remain controversial.

NEUROCHEMISTRY

Dopamine One of the most important observations in twentieth-century psychiatry is that dopamine antagonists ameliorate symptoms of schizophrenia. The implication that too much dopamine causes psychosis has dominated research for well over two generations and continues to exert a profound impact. In its most basic form, the dopamine hypothesis states that an excess of subcortical dopamine neurotransmission leads to psychotic symptoms. Observations that the prefrontal cortex modulates subcortical dopamine release have established a compelling link between cortical abnormalities and changes in the dopamine system. A current version of the dopamine hypothesis is that dopamine is dysregulated; levels may be reduced in the prefrontal cortex and altered in complex ways in subcortical and limbic regions. Reduced cortical dopamine could explain hypofrontality, impaired cognition, and negative symptoms (such as anhedonia and lack of motivation). Altered subcortical and limbic dopamine, on the other hand, could cause positive symptoms (such as hallucinations and delusions). Theories about the role of dopamine in schizophrenia have advanced in tandem with the increased understanding of the neurobiology of dopamine.

Neurobiology of Dopamine Dopamine (Fig. 12.4-4) is synthesized from tyrosine through dopa. The first step, the conversion of tyrosine to dopa by tyrosine hydroxylase, is the rate-limiting step, and is subject to feedback regulation. The major metabolic product of dopamine catabolism in humans is homovanillic acid, and, to a lesser extent dihydroxyphenylacetic acid and 3-methoxytyramine. Concentrations of these metabolites have been examined in the brain, cerebral spinal fluid (CSF), plasma, and urine of patients with schizophrenia to look for evidence of increased or decreased dopamine neurotransmission.

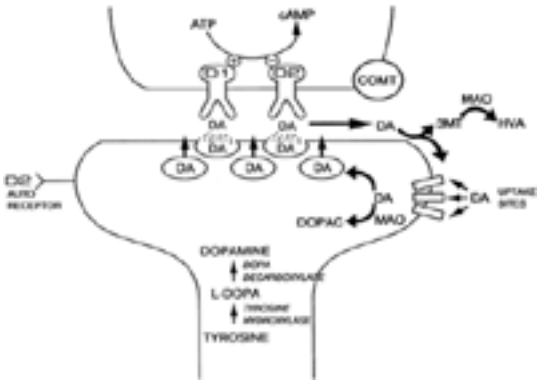


FIGURE 12.4-4 Dopamine metabolism and synaptic structure. In this schematic synapse, dopamine is released into the synaptic cleft where it can act on D_1 or D_2 postsynaptic receptors. Synaptic dopamine is inactivated by reuptake pumps or by catabolism via COMT and MAO. Presynaptic D_2 autoreceptors modulate dopamine synthesis and release in the striatum. (Drawn by Kyle Christensen.)

Dopamine cell bodies are primarily located in two midbrain nuclei: the substantia nigra (pars compacta) and ventral tegmental area. Projections from these nuclei have three primary target regions, and are named accordingly. The nigrostriatal tract carries nigral dopaminergic projections to subcortical motor control areas of the striatum (caudate and putamen in humans). The nigrostriatal projections come primarily from the substantia nigra but also, to a lesser extent, from the ventral tegmental area. Mesolimbic dopamine projections from this area target a number of limbic regions, such as the nucleus accumbens and temporal lobes. The mesocortical dopamine pathway projects primarily from the ventral tegmental area to the prefrontal cortex. A fourth dopamine tract is found entirely within the hypothalamus. In addition to different target regions, these separate projection systems function independently to some degree and are regulated by different mechanisms.

Dopamine exerts its effects through at least five receptor types, D_1 through D_5, identified on the basis of their deoxyribonucleic acid (DNA) sequence. Most pharmacological functions of dopamine receptors characterized so far are attributed to D_1 and D_2 receptors. Much less is known about the actions of D_3, D_4, and D_5 receptors. The D_1 family includes D_1 and D_5, while the D_2 family includes D_2, D_3, and D_4 receptors. Genes for the D_2 family have a number of introns, leading to alternative splicing and several isoforms. For example, the D_2 receptor has two common splice variants, a long and short form, usually both expressed in the same cell. The D_4 receptor has numerous polymorphisms, including longer and shorter forms, although these do not arise through alternative splicing. Different isoforms of the D_2 family may have different affinities for second messenger systems, presumably leading to variations in biological effects. Introns or alternative splicing variants for the D_1 family of receptors have not yet been identified.

D_1 and D_2 receptors are found predominantly on the primary efferent neurons of the striatum, and limbic system (e.g., the nucleus accumbens), prefrontal cortex, and other cortical regions. D_2 receptors are also located on the presynaptic dopamine terminals in target regions and dopamine cell bodies in the midbrain. These autoreceptors regulate dopamine synthesis, neuronal firing, and release. The latter two autoreceptors are not on mesocortical nerve terminals in the prefrontal cortex. D_3 receptors are expressed predominantly in subcortical limbic regions, such as the islands of Calleja and nucleus accumbens in the rodent, but are also seen in the hippocampus. D_4 receptors are thought to be presynaptic regulators of glutamate release on projections from cortical areas to the striatum and some limbic regions. D_5 receptors are found in limited distribution in the thalamus, hippocampus, and hypothalamus.

The role of the dopamine system in the overall economy of the brain is not well understood. The relation between dopamine cell loss and Parkinson's disease established its role in regulating motor activity. The link between dopamine and drugs of abuse suggest a critical role in motivation and reward. Increasingly sophisticated electrophysiological studies have shown that activation of subcortical dopamine pathways alert the organism to changes associated with the prediction of future salient and rewarding events. This function is essential for predicting future events, which allows an organism the ability to plan and control interactions with the environment. Furthermore, prefrontal cortical dopamine is critically

involved with working memory, a key component for higher-level information processing tasks. Thus, dopamine is involved in motor behavior, motivation, reward, and a variety of higher cognitive tasks, all of which have been implicated in schizophrenia. Clearly, the dopamine system has a complex molecular, cellular, and physiological neurobiology, and this underlies an equally complex functional role in normal brain and behavioral function.

Dopamine and Schizophrenia Evidence for the dopamine hypothesis of schizophrenia comes from a variety of sources. One approach has been to examine the effects of different medications on schizophrenic symptoms. Drugs that block D_2 receptors reduce psychotic symptoms; dopamine agonists worsen symptoms. These observations form the cornerstone of the dopamine hypothesis. A second approach has been to look at various indices of dopaminergic neurotransmission in patients with schizophrenia. Such indices include measures of presynaptic activity, such as the major dopamine metabolites, dihydroxyphenylacetic acid and homovanillic acid, as well as postsynaptic markers, primarily dopamine receptors. Metabolite studies have examined homovanillic acid in urine, plasma, CSF, and autopsied brain. Receptor studies have been performed on postmortem brain tissue and in living patients using PET and SPECT. More recent methods have been used to assess in vivo presynaptic dopamine levels and dopamine release using both PET and SPECT. Dopamine neurotransmission could be altered by changes in any one of a number of neuronal functions, including synthesis, degradation, release, uptake, receptor binding, or effects on second and third messenger systems. Although several decades of research have not provided definitive affirmation of the dopamine hypothesis, increasingly sophisticated methods to assess in vivo dopamine activity are beginning to yield important clues.

The notion that dopamine neurotransmission is increased in schizophrenia derives its most compelling support from clinical observations on the effects of drugs that impact psychotic symptoms. The introduction of antipsychotic medications in 1954 was a dramatic breakthrough in psychiatry and initiated an intense search for their mechanism of action. In 1963 antipsychotic medications were found to increase the concentrations of dopamine metabolites. It was suggested that increased metabolite concentrations were a compensatory response to the blockade of dopamine receptors by antipsychotic agents and a subsequent reduction in dopamine neurotransmission. The idea that these drugs reduced dopamine neurotransmission was further supported by the observation that they also induced parkinsonian adverse effects, symptoms that had recently been linked to the loss of midbrain dopamine neurons. In 1977, following pharmacological characterization of the D_2 receptor, a striking correlation was reported between the relative clinical potencies of all clinically available antipsychotic medications and their ability to block D_2 receptors. This landmark finding convincingly demonstrated that antipsychotic effects were mediated by D_2 receptor blockade.

While the correlation between clinical potency and D_2 blockade for antipsychotic medications was compelling, several problems emerged. D_2 blockade occurs within hours of administration, but the antipsychotic effects can take days or weeks to develop; this suggests that a secondary process is required. Studies of the chronic effects of neuroleptics then led to the observation that, after several weeks, dopamine neurons themselves stopped firing. After short-term administration of antipsychotic

medications there is an initial increase in dopamine neuronal firing as neurons attempt to overcome D_2 blockade; eventually this overexcitation leads to the phenomenon of depolarization block, where depolarized neurons simply stop firing. Reduced neuronal firing was thought to markedly reduce dopamine release, leading to reduced dopamine neurotransmission. For some time, the depolarization block theory was crucial in supporting the view that antipsychotic drugs exert their therapeutic effects by reducing dopamine neurotransmission. Subsequently, a number of studies have not found reduced dopamine release after long-term treatment with antipsychotic medication. While methodological issues are still debated, this suggests that some process other than a simple reduction in dopamine release may underlie the therapeutic effects of these medications.

Other observations have been difficult to reconcile with the dopamine hypothesis. For example, many symptoms such as cognitive deficits, anhedonia, and alogia typically fail to respond to treatment with antipsychotic medications, suggesting that other processes are involved. A second problem relates to the unique clinical effects of clozapine (Clozaril). Clozapine has been shown to benefit patients who do not respond to dopamine receptor antagonists. The dopamine hypothesis, on the other hand, implies that D_2 blockers should be equally efficacious. The unique clinical effects of clozapine suggest that it may have a different mechanism of action. Clozapine's effects have been attributed to several properties, such as its antagonism of serotonin receptors or its combination of D_1, D_2, and D_4 blockade. Drugs developed to mimic different aspects of clozapine's receptor-binding profile, such as risperidone (Risperdal), olanzapine (Zyprexa), and quetiapine (Seroquel), share some of clozapine's “atypical” characteristics.

A second line of evidence supporting the dopamine hypothesis comes from observing the effects of dopamine agonists. Chronic amphetamine abuse, for example, increases dopamine release and can lead to a psychosis similar to paranoid schizophrenia. Amphetamine-induced psychotic disorder, however, lacks other features associated with schizophrenia, such as negative symptoms and cognitive impairment. Furthermore, psychotic symptoms only develop after prolonged use (and typically at high doses), whereas dopamine neurotransmission is increased shortly after a single dose of amphetamine. This suggests that repeated increases in dopamine release produce secondary changes that are more directly responsible for the psychosis.

METABOLITE STUDIES The search for more direct evidence of altered dopamine release in schizophrenia led to investigations of dopamine and its metabolites in urine, plasma, CSF, and postmortem brain tissue. Consistent with the basic dopamine hypothesis, several studies of plasma homovanillic acid have found increases in unmedicated schizophrenia patients compared with controls. These studies sometimes report correlations between concentrations of homovanillic acid and severity of psychosis. Furthermore, antipsychotic medications appear to reduce plasma homovanillic acid over time, correlating with patients' improvement. Methodological problems, however, cloud the interpretation of studies using plasma homovanillic acid. It is unclear whether plasma homovanillic acid correlates with its concentrations in limbic brain regions, areas most likely to underlie the production of psychotic symptoms.

Investigators have also looked at dopamine metabolite levels in CSF. While most studies have failed to

find significant changes, several have reported a correlation between concentration of homovanillic acid and severity of psychotic symptoms. Studies of medication-free patients have tended to show a reduction in dopamine metabolites. Negative correlations have been found between concentrations of homovanillic acid in CSF and ventricular enlargement and severity of negative symptoms (e.g., anhedonia and flat affect). Prefrontal cognitive deficits have also been associated with reduced CSF homovanillic acid, perhaps consistent with a model of subcortical dopaminergic overactivity and prefrontal cortical hypoactivity; methodological issues make the interpretation of CSF studies problematic. First, dopamine and metabolite concentrations in the CSF are affected by a number of variables that are not commonly controlled. These include diet, time of day, height, and motor activity. Second, increased ventricular volume itself could affect the concentration of homovanillic acid. Third, CSF monoamine concentrations appear to have little relation to either regional brain levels of dopamine or, more importantly, to more direct measures of dopamine neurotransmission. Certainly if dopamine transmission in the prefrontal cortex is reduced and subcortical transmission is increased, it is difficult to predict what would happen to CSF concentration. Nevertheless, CSF data is often interpreted as supporting the notion that too much dopamine is related to positive symptoms whereas too little underlies negative symptoms.

More direct assessments of dopamine neurotransmission have come from postmortem studies of dopamine metabolites. Increased dopamine or homovanillic acid or both have been reported in a number of brain regions, although reports are often inconsistent. For example, one study found increased dopamine in the left amygdala, a second reported increases in the nucleus accumbens, and a third found increases in the caudate but not the accumbens. Increased homovanillic acid has been found in the cortex, accumbens, and caudate. The latter finding has been attributed to the effects of previous treatment with antipsychotic medications. At this point no clear consensus can be derived from studies of dopamine metabolites.

DOPAMINE RECEPTOR STUDIES A number of studies using postmortem brain tissue have shown increased numbers of D_2 dopamine binding sites in the brains of schizophrenia patients. A major confounding issue is whether this increase is a primary alteration in schizophrenia or secondary to long-term treatment with antipsychotic agents, known to cause rapid D_2 upregulation in animals. Studies in nonmedicated and medication-naive patients are conflicting. A number of studies of patients off medication for at least 1 month have found increased D_2 receptors, although several have not. It has been suggested that treatment with antipsychotic medications cannot account for the marked increase and bimodal distribution of D_2 receptors seen in patients who had been treated. Imbalances between D_1 and D_2 receptors have also been reported. Recent studies of D_3 receptors have suggested that D_3 mRNA may be processed abnormally in cortical neurons of patients with schizophrenia, resulting in reductions in the normal D_3 mRNA transcript. On the other hand, a postmortem study of striatal D_3 receptor binding found a significant increase in patients who were medication free for 1 month. D_4 receptors have been harder to assay because of the lack of specific ligands. While two reports using an indirect method have found evidence of increased D_4 receptor density, assays of mRNA for D_4 using highly specific antisense probes have not found increased levels.

Neuroimaging techniques have been used to measure indices of dopamine neurotransmission in living human patients. Striatal D_2 receptors have been assayed in medication-free patients by several groups using PET; the results, however, have been conflicting. One study found increased receptor numbers while two others did not. These studies used different PET ligands to measure D_2 receptor density, perhaps accounting for the conflicting results. One of the PET ligands binds only to D_2 and D_3 receptors; the second also binds to D_4 receptors. The discrepant PET findings have been attributed to an increase in D_4 receptors, consistent with postmortem studies. More recently, in vivo neuroimaging methods have been refined to assay presynaptic indices of dopamine storage and release. In this paradigm, radioactive D_2 ligand binding is examined at baseline and following a pharmacological challenge with amphetamine. The dramatic increase in dopamine release caused by amphetamine displaces the postsynaptic binding of the D_2 ligand. The washoff of the D_2 ligand can thus be used as an index of dopamine release. Unmedicated patients with schizophrenia show reduced ligand binding after amphetamine, but not at baseline. This suggests that patients with schizophrenia have increased synaptic dopamine following amphetamine. One explanation for this is that presynaptic stores may be increased; another possibility is that synaptic reuptake is reduced. Although methodological issues continue to be refined, this promising lead implies that subtle aspects of dopamine neurotransmission may be altered.

ANIMAL MODELS Animal studies have been invaluable in efforts to understand normal and abnormal function of the dopamine system. Of particular relevance for schizophrenia research are studies that attempt to model dysfunctional dopamine systems in a way that may shed light on the neurobiology of psychosis.

Initial attempts to develop relevant animal models began with repeated, high doses of stimulants (such as amphetamine), based on the association between stimulant abuse and psychosis in humans. Repeated stimulant treatment was also thought to model repeated stress, an apparent trigger of psychotic relapse. Remarkably, stimulants increase the sensitivity of the mesolimbic dopamine system to stress, a process referred to as *sensitization*. Furthermore, in some paradigms stimulants can reduce presynaptic indices of dopamine activity, which has led to speculations that repeated increases in dopaminergic transmission (e. g., from stress) could lead to sensitization in limbic regions and long-term dopamine depletion in prefrontal regions. Thus, long-term administration of stimulant may provide a model to explore the interactions between known triggers of psychosis and dysfunctional dopamine systems.

Another promising line of animal research suggests that alterations in dopamine neurotransmission in one region may be secondary to primary deficits in another. For example, depletion of dopamine from prefrontal regions can increase dopamine metabolism in the striatum of rats. This suggests that a primary reduction of prefrontal dopamine in humans could theoretically lead to secondary alterations in subcortical dopamine. Reduced prefrontal dopamine could certainly explain the hypofrontality and negative symptoms that characterize schizophrenia. Although no direct evidence has shown that there are dopamine abnormalities in these regions, the indirect evidence reviewed above is suggestive. In a related line of research, structural damage to cortical and limbic regions has been shown to change subcortical dopamine neurotransmission. For example, within the limbic system lesions of the hippocampus or amygdala alter dopamine neurotransmission in the nucleus accumbens and prefrontal

cortex. Such observations have been critical in attempts to relate structural and functional changes in frontal, temporal, and hippocampal regions with abnormalities in the dopamine system. They suggest that information-processing deficits in frontal and limbic regions have marked effects on subcortical processes, including dopamine neurotransmission.

The dopamine hypothesis continues to exert a profound effect on research in schizophrenia. The discovery of new subtypes of dopamine receptors along with new neuroimaging approaches offer improved methods to study the function and pathophysiology of this system in humans. Particularly important for schizophrenia research is the finding that dopamine subsystems are interconnected and that damage to different brain regions previously implicated in schizophrenia can have marked effects of dopamine neurotransmission. At present, a variety of indirect data suggest that prefrontal dopamine neurotransmission may be reduced whereas subcortical dopamine is dysregulated in schizophrenia. Whether these changes are real and whether they are secondary to cortical or limbic dysfunction remains to be seen.

Glutamate Interest in glutamate's role in the pathophysiology of schizophrenia has developed relatively recently. This interest was spurred primarily by two observations. First, acute ingestion of phencyclidine (PCP), a glutamate antagonist, produces a syndrome similar to schizophrenia. Second, glutamate is an essential neurotransmitter in those neural networks that may be involved in schizophrenia. Subsequently, a variety of postmortem and clinical data have been garnered in support of a glutamatergic abnormality.

Neurobiology of Glutamate Glutamate is one of the most prevalent neurotransmitters in the brain. Virtually all neurons in the brain are affected when glutamate is applied. A nonessential amino acid that does not cross the blood-brain barrier, it can be synthesized in the brain from glutamine. The dominant mode of inactivation of synaptic glutamate is via reuptake by specific, high-affinity uptake sites.

The four classes of glutamate receptors have been identified and named after their affinity for specific ligands: *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA), kainic acid (KA), and L-aminophosphono-butyric acid (AP4). The first three are ionotropic receptors; their effects are mediated by changes in ionic conductance through neuronal membranes, including sodium, potassium, and calcium. The ionotopic receptors have been implicated in neurotoxicity following ischemia, mediated in part by increased intracellular calcium influx and apoptosis. The NMDA receptor is functionally different from the others and has been implicated in long-term potentiation (a process related to memory) in the hippocampus. Paradoxically, NMDA blockade can also result in neurotoxicity, apparently modulated by interneurons and activation of non-NMDA glutamate receptors. The last type of glutamate receptor, labeled by AP4, is a metabotropic receptor, a member of the family of G-protein–linked receptors. The metabotropic receptors modulate activation of second messengers, such as phospoinositide and cyclic adenosine monophosphate (cAMP), which can produce long-term, modulatory effects. Major advances in understanding the molecular biology of these receptors is increasing the understanding of their function.

The NMDA receptor is a complex protein that has particular relevance for schizophrenia research.

Blockade of the NMDA receptor by phencyclidine (PCP), a noncompetitive antagonist, produces symptoms similar to those seen in schizophrenia. NMDA receptor activation is excitatory, reducing postsynaptic membrane potential. PCP binds to a site within the open NMDA ion channel, thus blocking ionic flux. The mechanism by which NMDA antagonism produces psychotic symptoms is unclear; one theory is that NMDA antagonists exert their psychotomimetic effects via NMDA receptors' role in regulating striatal and limbic dopamine neurotransmission. Of note, NMDA receptor density is highest in the hippocampus and prefrontal cortex, two areas already implicated in the pathophysiology of schizophrenia. Altered neurotransmission in these regions could also play a role in PCP's effects.

The NMDA receptor has a number of modulatory sites that regulate ionic conductance. Endogenous modulators include glycine, zinc, magnesium, and the polyamine spermidine. The glycine modulatory site has become a target for drug development. Increasing NMDA neurotransmission by increased glycine binding has been hypothesized to reduce symptoms of schizophrenia. Several studies have attempted to do so using glycine agonists such as milacemide or cylcoserine, and the results have been mixed. Another potential pharmacological target is the high-affinity glycine uptake pump. Antagonists of this site should increase synaptic glycine concentrations, enhancing NMDA neurotransmission. Similarly, antagonists of the glutamate reuptake pump could boost NMDA receptor activation. It is unclear whether ongoing efforts to develop antagonists at these sites will lead to therapeutic agents for patients with schizophrenia. A major difficulty with increasing NMDA neurotransmission is its narrow range of physiological responsivity. If NMDA stimulation is too high, seizures or neurotoxicity can result.

Glutamate is relevant to the neurochemistry of schizophrenia because of its role in key neural networks. Projections to and from cortical and hippocampal pyramidal neurons use glutamate as a primary neurotransmitter. These include projections to subcortical structures such as the striatum, nucleus accumbens, and ventral tegmental area; output from these areas is strongly modulated by glutamate. Thalamic projections to the cortex also employ glutamate as the major neurotransmitter. Glutamate neurotransmission is important not only for rapid synaptic transmission between these regions, but also for experience-dependent cortical plasticity and memory. This is particularly true for the voltage-sensitive NMDA receptor, a likely candidate for modulating memory traces at Hebbian synapses. Glutamate's essential role in key neural networks, memory and cortical plasticity, thus make it a likely candidate for involvement in altered information processing in schizophrenia.

Glutamate in Schizophrenia Acute intoxication with the NMDA antagonist, PCP, produces hallucinations, thought disorder, negative symptoms, and cognitive deficits. In comparison, dopamine agonists, such as amphetamine, primarily induce paranoid delusions, and only after long-term use. The differences in these drug-induced psychoses suggest that glutamatergic neurotransmission could be more proximal to the pathological processes mediating psychosis. The search for more direct evidence has focused on CSF and postmortem studies of brain tissue.

Studies of glutamate levels in CSF and brain have been mixed. An initial, pioneering study of CSF found low levels of glutamate in patients compared with controls. Possible methodological problems make this data difficult to interpret, however, and three subsequent studies have been unable to replicate

the finding. Two studies have looked at glutamate levels in postmortem brain tissue. One found no differences whereas the other found specific reductions in the hippocampus and prefrontal cortex in patients with schizophrenia. The latter study also looked at a neuropeptide co-localized with glutamate *N*-acetylaspartylglutamate [NAAG]. The NAAG pathway has recently been identified as an important comodulator of glutamate neurotransmission. The reported changes in NAAG and its metabolism in brains of patients with schizophrenia open up a provocative new area to explore possible alterations in glutamate neurotransmission.

Postmortem receptor studies have been more promising. In general, these studies have tended to find increased receptor binding in prefrontal regions and reductions in temporal areas. Two reports have found increased kainate binding in the medial frontal cortex; a third found increases in orbitofrontal NMDA receptors. An increase of prefrontal cortical glutamate uptake sites has also been described. A recent molecular study using in situ hybridization and probes for all five NMDA receptor subunits, while not finding an overall increase in receptor mRNA did find a 53 percent increase in the expression of a subunit (NR2D), suggesting a change in the functional properties of prefrontal NMDA receptors.

In the temporal lobe, several abnormalities of the glutamate system have been published. Autoradiographic studies have reported that KA receptor binding is reduced, particularly in the hippocampus. Consistent with this finding, reduced expression of mRNA for receptor subunits has been found in temporal lobe areas. Reduced density of temporal lobe AMPA receptors has been seen, but less consistently. In a recent extension of this work, mRNA transcripts for *Glu* R1 and *Glu* R2 were assayed; these transcripts code for AMPA receptor subunits. Consistent with receptor studies, reductions were seen in the hippocampus and other temporal lobe areas. Finally, the glutamate reuptake site has been assayed in the temporal lobe as an index of presynaptic glutamate terminal number. Reduced levels of mRNA for the reuptake site suggest a possible reduction in terminal number and thus in axonal projections. Regarding other brain regions, some receptor studies have performed on material from the basal ganglia. Increases in AMPA receptors and reduced NMDA receptors have been reported; some, studies, but not all, have found reduced glutamate uptake sites.

Taken together, the postmortem literature is notable for a myriad of findings implicating alterations in glutamatergic neurotransmission. However, given the typical small number of brains studied and large number of variables, replication of specific findings is critical. Some have theorized that there is a loss of glutamatergic neurons in temporal areas, consistent with structural neuroimaging findings of reduced volume. In this schema, increased glutamate receptors in the cortex and putamen are hypothesized to be secondary to reduced glutamatergic inputs or neurotransmission. The increased focus on glutamate in postmortem studies will bring increasingly sophisticated assessment of this neural system.

Serotonin The idea that serotonin may play a role in schizophrenia was first postulated when the hallucinogen lysergic acid diethylamide (LSD) was found to block serotonin receptors. Since then, basic studies have begun to unravel the surprising complexity of this system and have provided new targets for investigation. Studies of schizophrenia have looked at a variety of parameters, including plasma serotonin levels, brain receptor levels, and clinical response to serotonergic drugs. Two findings are particularly promising: first, data from postmortem studies have found changes in frontal cortical

receptor number; second, new “atypical” antipsychotic medications that are both serotonergic and dopaminergic antagonists appear to have clinical advantages over pure D_2 antagonists. These developments have increased the focus on serotonin in schizophrenia.

Basic Neurobiology Serotonin (5-hydroxytryptamine) is synthesized from tryptophan and is broken down into 5-hydroxyindolic acetic acid (5-HIAA) by monoamine oxidase (MAO). Tryptophan is an essential amino acid; dietary intake of tryptophan can affect CNS synthesis of serotonin. Serotonin synthesis is also modulated by autoreceptors on nerve terminals. Synaptic serotonin is inactivated primarily by reuptake pumps on presynaptic neurons and glia; following uptake, serotonin is repackaged into vesicles or broken down to 5-HIAA. Both serotonin itself and its uptake pumps are found in blood platelets, where they play a role in clotting. In the CNS, serotonin neuronal cell bodies are located in the brainstem in nine separate nuclei. Axons from these cells project through the median forebrain bundle to virtually all regions of the CNS, including the cortex, limbic regions, and the striatum.

The effects of serotonin are mediated by an ever-increasing number of receptor subtypes. Currently, seven classes of serotonin receptors have been characterized: serotonin (5-hydroxytryptamine [5-HT])-type 1 (5-HT_1) through 5-HT_7. Ten subtypes have been described in the 5-HT_1 family (5-HT_{1a} through 5-HT_{1e}), three in the 5-HT_2 family (5-HT_{2a} through 5-HT_{2c}) and one for 5-HT_3. Most relevant for schizophrenia are the 5-HT_2 and 5-HT_3 subtypes. 5HT_2 receptors are found in the prefrontal cortex, striatum, and nucleus accumbens; 5-HT_3 receptors are found in cortical, limbic, and subcortical areas, such as the amygdala and hippocampus.

The serotonin system subserves a bewildering array of physiological and behavioral functions. For example, somatodendritic 5-HT_2 receptors regulate dopaminergic neuronal firing. Striatal nerve terminal serotonin receptors inhibit dopamine release. Behaviorally, serotonin has effects on cardiovascular, respiratory and motor activity, emesis, sexual behavior, aggression, anxiety, mood, and pain. Frontal serotonin, in concert with dopamine, may play an important role in the modulation of attention and arousal. Recently, basic research using aplysia has shown that serotonin plays a critical role in synaptic mechanisms associated with learning and memory; it may also have important neurotrophic effects during development and in the adult organism.

Serotonin in Schizophrenia The earliest studies to examine serotonin in schizophrenia looked at peripheral measures, such as serotonin concentrations in plasma and uptake in platelets. These studies found increased concentrations in plasma and, less consistently, reduced uptake in platelets. Studies of CSF metabolites have been mixed and suffer from the same methodological confounds described for dopamine. More direct measures of CNS neurotransmission include postmortem assays of serotonin activity, including concentrations in brain tissue; receptor-binding density; reuptake site binding; and levels of mRNA for receptor subtypes, reuptake sites, and synthetic enzymes for serotonin itself.

Although there have been multiple reports of abnormal serotonin levels in a variety of neural structures, only two findings have been replicated: increased levels in the putamen and increased levels in the

globus pallidus. One difficulty with this approach is that measurement of neurotransmitters and their metabolites is notoriously unreliable because of their instability in postmortem tissue. In comparison, receptors, reuptake sites, and the mRNA for receptors, reuptake sites, and synthetic enzymes are more stable. Of studies looking at these parameters, the 5-HT_2 subclass has received the most attention. Following an initial report of a reduction in prefrontal cortex in the density of this receptor, two other research groups replicated this finding although a third did not. Whereas this abnormality may be intrinsic to schizophrenia, it is also possible that reduced 5-HT_2 receptor density is a consequence of therapy with antipsychotic drugs. The density of reuptake sites for serotonin also appear to be reduced in schizophrenia, particularly in frontal and anterior cingulate cortices.

Studies looking at the mechanism of action of atypical antipsychotic drugs, such as clozapine, have fueled much of the recent interest in serotonin's role in schizophrenia. Clozapine has a variety of therapeutic properties different from the dopamine receptor antagonists. These could be due to clozapine's ability to block 5-HT_{2a}, 5-HT_{2c}, 5-HT_3, 5-HT_6, or 5-HT_7 receptors, or to increased serotonin release in the prefrontal cortex. When one compares serotonin-dopamine antagonists, which share some of clozapine's properties, such as the reduced liability to produce parkinsonian symptoms, two impressive similarities are their 5-HT_2-binding affinity and the ratio of 5-HT_2 to D_2 binding. This suggests that serotonergic antagonist properties may account for the improved adverse effects profile and perhaps also the enhanced therapeutic efficacy often attributed to the serotonin dopamine antagonists.

In summary, both postmortem studies and drug trials using 5-HT_2–D_2 antagonists suggest that serotonin may play an important role in schizophrenia. Data implicating frontal and anterior cingulate cortices are particularly striking. It is unclear, however, whether alterations in serotonin neurotransmission are primary or secondary and how they may relate to the other neurobiological processes described. Some preliminary investigations suggest that maternal exposure to toxins can produce long-term changes in serotonin neurotransmission. This raises the possibility that neurodevelopmental insults could alter serotonin neurotransmission in adults. Researchers interested in the mechanisms of amphetamine-induced behavioral sensitization have also begun to suspect that serotonin may play a significant role. If sensitization were to be involved in schizophrenia, as has been suggested, serotonin could be a factor. Although research in serotonin has typically taken a backseat to research on dopamine, its relevance for schizophrenia continues to increase as more is revealed about its many neurobiological properties.

Other Neurotransmitters A wide variety of additional neurochemical systems have been studied in schizophrenia, several of which are noteworthy because of potentially interesting findings or because of how extensively they have been studied. These include GABA, norepinephrine, neurotensin, and cholecystokinin. As with other neurotransmitters, studies of these systems have typically looked at transmitter and metabolite levels in brain, CSF, or plasma, as well as receptor protein and mRNA expression in specific brain regions.

GABA Particularly intriguing is research into the role of GABA, which is the major inhibitory neurotransmitter in the brain. Virtually all neurons are inhibited by GABA, and up to 40 percent of

neurons use GABA as their major neurotransmitter. Many GABA neurons are local inhibitory interneurons, but GABA neurons in some regions (such as the striatum) are also primary efferent neurons. GABA is synthesized from glutamate via the enzyme glutamic acid decarboxylase (GAD). GABA acts at two receptor subtypes, $GABA_A$ and $GABA_B$, the former being the more important in the CNS. A variety of drugs act at GABA receptors, including alcohol, benzodiazepines, and barbiturates. Findings implicating GABA in schizophrenia include reduced number of GABAergic cortical interneurons, increased $GABA_A$ receptor density in the prefrontal cortex, and reduced GABA uptake sites in the hippocampus. All three findings are consistent with reduced GABA cell number or GABA neurotransmission. Studies of mRNA have found reduction in prefrontal GAD mRNA but not in prefrontal $GABA_A$ receptor mRNA. The former is consistent with reduced GABA neuronal activity; the latter is not. This preliminary effort suggests that GABA cell number or activity is reduced in schizophrenia. As with other postmortem findings, however, further replication is necessary before they can be accepted with confidence.

Norepinephrine Norepinephrine, another monoamine neurotransmitter, has been intensively studied in schizophrenia, although interest has waned recently. Similar to dopamine and serotonin, norepinphrine neurons are located in the brainstem in a group of nuclei (including the locus ceruleus) that project to a variety of cortical and subcortical regions. Norepinephrine acts at two receptor families, adrenergic and β-adrenergic receptors; at least seven α and three β subtypes have been cloned. Both receptor families exert their effects via changes in G-protein–mediated second messenger systems, including cAMP and phosphoinositol. Two neuropeptide transmitters, galanin and neuropeptide Y, are colocalized in noradrenergic neurons. Norepinephrine and its co-transmitters are involved in a number of physiological and behavioral processes including the sleep-wake cycle, arousal, stress, and memory. Both basic and clinical studies support a role for this system in psychiatric disorders such as anorexia nervosa, bulimia nervosa, anxiety disorders, post-traumatic stress disorder, depressive disorders, substance dependence, and substance withdrawal. Many of the behavioral states mediated by the noradrenergic system are markedly altered in schizophrenia, suggesting a role here as well. However, more direct evidence is lacking and any changes in noradrenergic function in schizophrenia may be secondary to the agitation that frequently accompanies psychosis.

Initial studies of norepinephrine examined concentrations in plasma, CSF, and brain tissue. Both plasma and CSF concentrations of norepinephrine and its metabolite appear to be increased in patients with schizophrenia, although this has not been a consistent finding. Concentrations are reduced with treatment with antipsychotic agents and are correlated with clinical improvement. Recently, increased plasma concentrations have been associated with deficit symptoms whereas reduced plasma levels have been associated with depressive symptoms. These two findings seem contradictory and cast doubt on the usefulness of this approach. Furthermore, conclusions from such studies are limited by the same methodological pitfalls described above for other neurotransmitters, including the confounds of treatment with antipsychotic agents and the meaning of peripheral measures. Studies of brain norephinephrine and its receptors have been mixed, with some finding elevations and others finding no changes. The clinical effects of adrenergic agents have generally not been impressive. At least one report found that the presynaptic α_2-adrenergic receptor agonist clonidine (Catapres) reduces psychotic

symptoms, presumably by reducing norepinephrine release. On the other hand, several other studies did not find this effect, and at least one group has reported therapeutic effects for an α_2-adrenergic receptor antagonist, idazoxane. Finally, a number of genetic association studies have looked at the incidence of polymorphisms for genes related to norepinephrine neurotransmission, including dopamine beta hydroxylase and the norepinephrine transporter. Although relatively common polymorphisms have been reported for both, no association with schizophrenia has been reported.

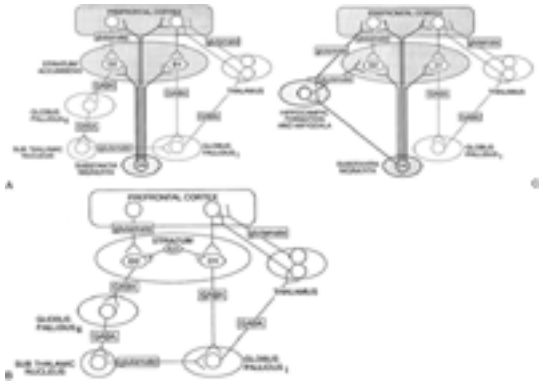
Neuropeptides Two other interesting candidate molecules that have been studied in schizophrenia are the neuropeptides cholecystokinin and neurotensin. Both are found in a number of brain regions implicated in schizophrenia, such as the substantia nigra, nucleus accumbens, hippocampus, and various cortical regions. Both are colocalized with dopamine, GABA, glutamate, and other neurotransmitters. Several studies have reported changes in the levels of the peptides themselves, mRNA, or receptors. For example, the following findings have had some degree of replication: reduced temporal lobe cholecystokinin peptide concentrations, reduced cholecystokinin receptor density in both temporal and frontal regions, and reduced cholecystokinin mRNA in the temporal lobe. In general, further replication is required. Drug trials with the cholecystokinin agonist ceruletide have been mixed. Several open trials were promising, but double-blind trials were not. Unfortunately, it is not certain that ceruletide crosses the blood-brain barrier.

Neurotensin's appeal is due in part to its endogenous antipsychotic-like properties. Not only is it colocalized in dopaminergic neurons, but infusions of neurotensin into the nucleus accumbens block the excitatory effects of stimulants and reduce behavioral activation. Neurotensin levels in the nucleus accumbens are markedly increased by treatment with antipsychotic medication. CSF studies have shown reduced neurotensin concentrations and correlations between reduced concentrations and increased psychopathology in drug-free patients with schizophrenia. However, postmortem studies have not shown differences between patients and controls in concentrations of the peptide itself. Such studies are confounded by the pronounced effects of antipsychotic drugs on central nervous system (CNS) neurotensin. One recent report found a 40 percent reduction of neurotensin receptors in the entorhinal cortex in patients with schizophrenia. Further replication and exclusion of effects of treatment with antipsychotic agents will clarify the significance of this finding.

NEURAL CIRCUITS

The variety of structural, functional, and neurochemical abnormalities described implicate disordered information processing in several interconnected neural pathways in patients with schizophrenia. A description of the anatomical components of these pathways and their possible function will provide a basis for integrating the many abnormalities noted in schizophrenia (Figs. 12.4-5).

FIGURE 12.4-5 A, Neural networks implicated in the neurobiology of schizophrenia. Cortico-striatal-thalamic pathway. Prefrontal glutamatergic projections synapse on GABAergic striatal neurons that



express either D_1 or D_2 receptors. The independent D_1 and D_2 pathways are referred to as the direct and indirect pathways respectively. They have separate efferent pathways projecting to either the globus pallidus, pars externa = E, or pars interna = I. Both pathways ultimately project back to the anterior thalamus. **B**, Ascending dopamine projection pathways modulate circuits in A. Dopamine neurons (DA) from the substantia nigra tend to project mainly to the striatum, while the adjacent ventral tegmental area DA neurons projects primarily to the prefrontal cortex, ventral striatum, and limbic regions. **C**, Limbic projections to circuits from **A** and **B**. The hippocampal formation and amygdala project to the prefrontal cortex and ventral striatum. They receive glutamatergic cortical input and dopamine projections from the VTA. (Drawn by Kyle Christensen.)

As cortical abnormalities have played a dominant role in theories of schizophrenia, understanding the functional connectivity of these areas is important. One of the most intensively studied pathways is the cortico-striato-thalamic loop. The prefrontal cortex, the most highly and recently evolved part of the primate brain, sends a massive glutamatergic projection to subcortical regions, most notably the striatum (putamen and caudate in humans). The striatum in turn sends GABAergic projections through a number of downstream basal ganglia nuclei that ultimately feed into the anterior thalamus. Completing the loop, the anterior thalamus sends a massive glutamatergic projection back to the prefrontal cortex. Several salient features are noteworthy. First, this loop appears to consist of at least five separate but parallel channels processing different types of information (such as cognitive, emotional, and motoric information). Second, output from the striatum is split into two opposing, counterbalancing pathways. The so-called direct and indirect loops are modulated by D_1 and D_2 receptors, respectively. Their coordinated output modulates information returned to the cortex via the anterior thalamus. Third, within the striatum itself, the ventral portion (commonly referred to as the *nucleus accumbens*) receives predominantly limbic inputs, while dorsal regions receive inputs more relevant for motor function. This functional segregation is maintained in downstream projection regions.

A second important system that modulates activity of the cortico-striato-thalamic pathway is the dopamine system. Dopamine neurons in the substantia nigra and ventral tegmental area project to the striatum, nucleus accumbens, and prefrontal cortex. Dopamine modulates cortical output to the striatum via input to glutamatergic pyramidal neurons. In the striatum, dopamine axons synapse on the primary output neurons, the medium-sized, spiny, GABAergic neurons. Coordinated cortical and subcortical dopamine neurotransmission may be important for normal information processing through this loop. Furthermore, dysfunction in one area may produce changes in another. For example, lesions of the prefrontal cortex can induce alterations in subcortical dopamine neurotransmission.

A third neural system interacting with the first two is the limbic system. This complex system involves hippocampus, amygdala, thalamus, hypothalamus, and cingulate gyrus, among others. This immense

circuit, subserving functions related to memory and emotional experience, among many others, has direct projections to both prefrontal cortex and ventral striatum. The prefrontal cortex has reciprocal projections back to the mesial temporal lobe and hippocampus. The hippocampus, amygdala, and cingulate have important projections to the ventral (or limbic) aspect of the striatum. This area, in turn, projects to the thalamus via the ventral aspect of the globus pallidus, the pars interna. In this way, three major brain regions—the cortex, limbic system, and basal ganglia—communicate and interact. Information-processing abnormalities in one area, such as in the hippocampus, would have significant downstream effects on other regions, such as prefrontal cortex and striatum.

Structural and functional measures have implicated some abnormality in all three components of these interacting systems. It is uncertain which are primary and which are secondary. It seems very possible that different types of lesions could alter the function of individual components, which could then produce secondary downstream changes in connected circuits.

NEUROBIOLOGICAL MODELS

The essential neurobiological features of schizophrenia may place some constraints on plausible pathophysiological processes. First, there is a major genetic contribution. Many genes are likely to be involved and these may function in part by increasing vulnerability to the deleterious effects of environmental factors. Several environmental factors have been hypothesized to increase the risk of schizophrenia, perhaps by producing subtle brain damage. Structural abnormalities have played an important role in placing theoretical constraints on mechanisms. Since they are present from early in the illness and do not appear to progress, they may predate the onset of illness. Neuropathological data and studies of obstetric and perinatal complications support the idea that an early lesion may account for structural changes. The apparent lack of gliosis in postmortem studies is particularly critical and implicates in utero factors. Structural and functional neuroimaging, as well as neuropsychological data and animal studies present converging evidence for the importance of frontal and temporal regions. Finally, altered dopamine and glutamate neurotransmission are likely to play a part in the expression of psychotic symptoms.

The neurodevelopmental model can account for many of these findings. In short, some process (genetic or environmental) produces damage to selected brain areas early in life. Temporal lobe regions such as the hippocampus may be particularly vulnerable. Secondary functional abnormalities develop later. As the prefrontal cortex matures in late adolescence, the behavioral and cognitive sequelae of subtle structural deficits become manifest. One result is hypofrontality and cognitive impairment. Alterations in limbic and prefrontal function then produce downstream, secondary alterations in subcortical dopamine, glutamate, and other neurotransmitter systems. Dopamine dysfunction, in particular, may lead to positive psychotic symptoms. The feasibility of this model has received substantial validation from animal studies showing the delayed behavioral and neurobiological effects of minor damage to the hippocampus in neonatal rats. Observations that children at risk for schizophrenia have a number of subtle neuropsychiatric abnormalities, such as deficits in attention, motor control, and social interactions, also support the neurodevelopmental model.

Although the neurodevelopmental hypothesis has been an important organizing heuristic since the mid-1980s several critical issues remain unresolved. First, it remains unclear when structural abnormalities actually develop. Finding such abnormalities in young children who go on to develop schizophrenia would offer strong support for this hypothesis. Alternatively, if these abnormalities develop later in life (e.g., in mid-adolescence), other mechanisms would be implicated. For example, it is unclear whether dendritic "pruning" or an apoptotic mechanism could account for volumetric reductions in areas such as the hippocampus. Observations of reduced neuronal size suggest that factors regulating this parameter could play a role. Second, despite the myriad of findings, the lack of any consistently replicable neurodevelopmental lesion in postmortem studies continues to leave the issue in doubt. It is entirely possible that no single lesion exists. Third, the issue of heterogeneity remains unresolved. Although patients with schizophrenia have structural and functional alterations as a group as compared to controls, it remains unclear whether these are necessary features of the illness. Certainly many patients are in the normal range in some or many of these measures. The same is true for most neurodevelopmental parameters. Many patients have completely normal or even above-average function in childhood and adolescence. Most patients with schizophrenia have no known history of pregnancy, obstetric, or neonatal insults. Is it possible that different patients have abnormalities restricted to differing prefrontal, temporal, or subcortical areas? Such primary lesions could induce secondary dysfunction in connected regions. Fourth, the delayed onset of psychosis presents some problems for the neurodevelopmental model. Although onset is typically in the early 20s, some patients do not develop symptoms until the fourth or even fifth decade of life. It seems most likely that such cases involve mechanisms other than or in addition to neurodevelopmental processes.

Several alternative models have been put forward to deal with some of these problems. For example, structural abnormalities could develop in adolescence, very early in the illness. It is unclear what could account for this, but candidate mechanisms might include reduction in neuronal size or excessive dendritic pruning. Neurotransmitter abnormalities, such as in the dopamine and glutamate systems, may follow. Another possibility is that some cases of schizophrenia are due to increased stress associated with entry into adulthood. This could trigger dopamine abnormalities in genetically vulnerable individuals. Structural abnormalities, in these cases, could be nonspecific vulnerability factors or could be secondary to psychosis itself. A third possibility is that schizophrenia is a heterogeneous illness with several dimensions, none of which is necessary or sufficient. Different domains could involve neurodevelopmental cortical dysfunction, dopamine and glutamate function, cortical regulation of dopamine, and interdependent functioning of a myriad of heteromodal cortical neural networks. In this model, a complex web of genetic and environmental factors could impact on these many neural networks.

One approach toward settling this issue is to examine neurobiological traits associated with schizophrenia. Such traits may be closer to the underlying physiological deficits induced by genes associated with the illness. As such, these traits may have a simpler genetic architecture, making it easier to detect their genes in linkage studies. A number of potential phenotypes have been identified that are clearly familial and thus may have a significant genetic basis. These include impaired sensory gating, eye-tracking dysfunction, perceptual aberrations, schizotypal symptoms, attentional impairment, deficit symptoms, structural brain abnormalities, and cognitive deficits. The feasibility of this approach has

been validated by a recent report of linkage using a measure of impaired sensory gating. Suppression of the auditory p50 wave in a sensory gating paradigm has been linked to 15q13–14. This is very close to the α7 nicotinic cholinergic receptor, previously implicated in impaired p50 suppression. Several other preliminary reports have used eye tracking and positive psychotic symptoms. The use of such intermediate phenotypes may also reveal genes that are more important to functional outcome. Unfortunately, the heritability and genetic architecture of most intermediate phenotypes are uncertain, despite a wealth of data showing that many such traits are familial. Studies to assess these parameters and attempt linkage will require phenotyping large numbers of patients.

The underlying neurobiology of schizophrenia remains a mystery. Genetically, the disorder is complex, confounding efforts to locate causative genes. Similarly, the effects of environment are subtle, with no clear major factor emerging. Pregnancy, labor, and delivery complications may play a limited role. Increasingly sophisticated techniques, guided by greater understanding of basic neurobiology, are being used to uncover alterations in a number of brain parameters. Neurobiological abnormalities include reduced volume of several brain structures, sulcal widening, and increased ventricular size. Cortical abnormalities, particularly in the prefrontal and temporal cortices, have also been implicated by cognitive testing and functional neuroimaging. Postmortem studies have failed to find a major lesion or gliosis that could account for structural abnormalities. They have, however, detected a variety of subtle cytoarchitectural changes, perhaps caused by abnormal neurodevelopment. Several neurotransmitters, including dopamine, glutamate, and serotonin, have been implicated. The putative structural, functional, and neurochemical abnormalities can be understood in the context of the neural systems they comprise. These include cortical-striatal-thalamic loops, ascending dopamine projection pathways, and the limbic system. Interconnections between these systems make it difficult to determine which lesions are primary and which are secondary.

The neurodevelopmental model has been a critical organizing heuristic that synthesizes these seemingly disparate observations. This theory suggests that nonspecific lesions in early life, perhaps in utero, produce subtle behavioral manifestations in childhood. The onset of psychosis is delayed until brain maturation reaches later stages in late adolescence. Many questions remain unanswered, however, leaving some aspects of this theory in doubt. Combining techniques such as neuroimaging with molecular genetics provide fertile areas for future research to separate the strands that make up the tangled web of schizophrenia.

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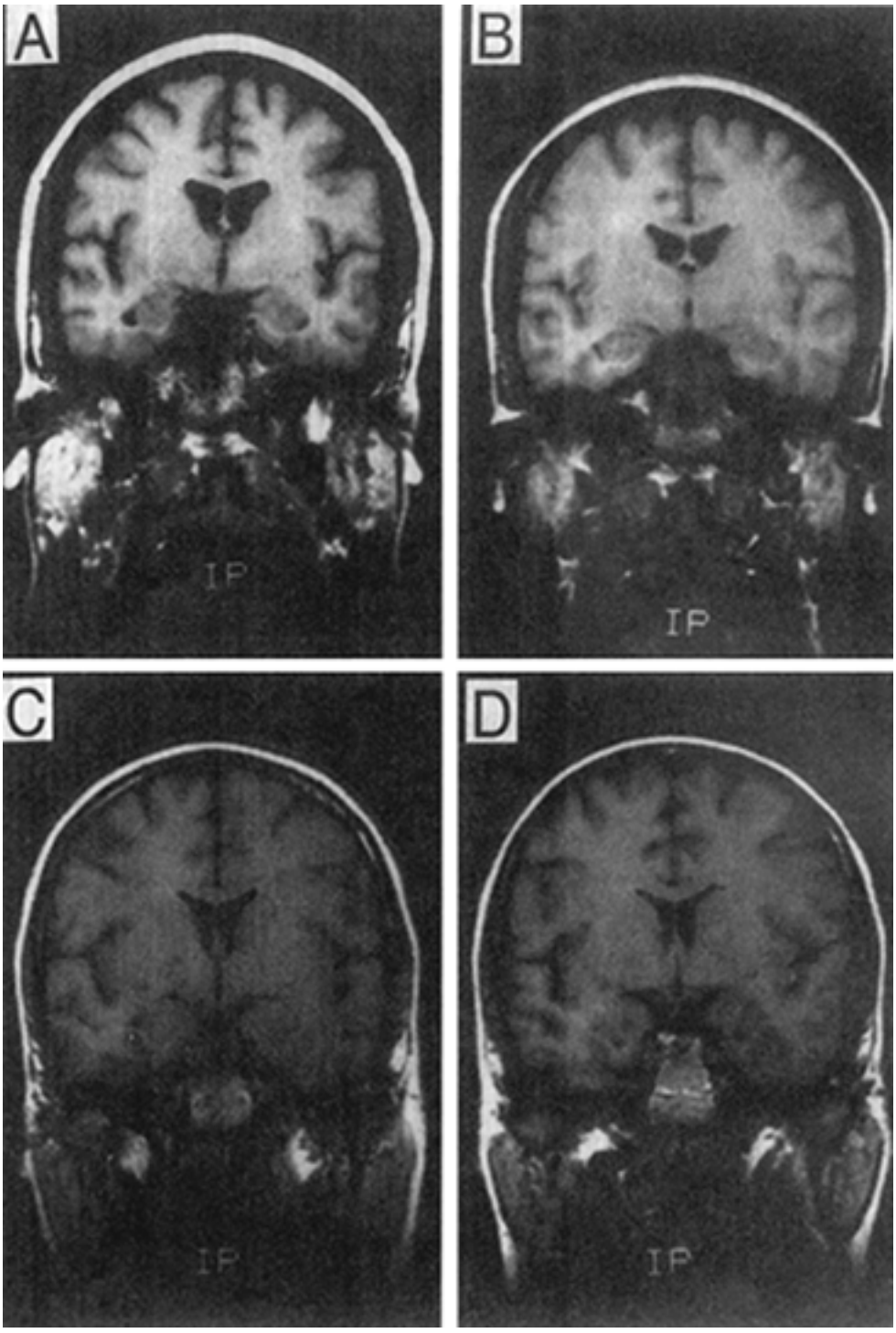

FIGURE 12.4-1 MRI scans (coronal sections) of two sets of discordant monozygotic twins (**A** and **B** = set 1; **C** and **D** = set 2). For each pair, one has schizophrenia (**A** and **C**) while the other does not (**B** and **D**). For both pairs, the affected twin has larger ventricles than the unaffected twin, even though ventricular size appears to be within the normal range for the affected twin (C). (Courtesy of D. Weinberger and E. F. Torrey.)

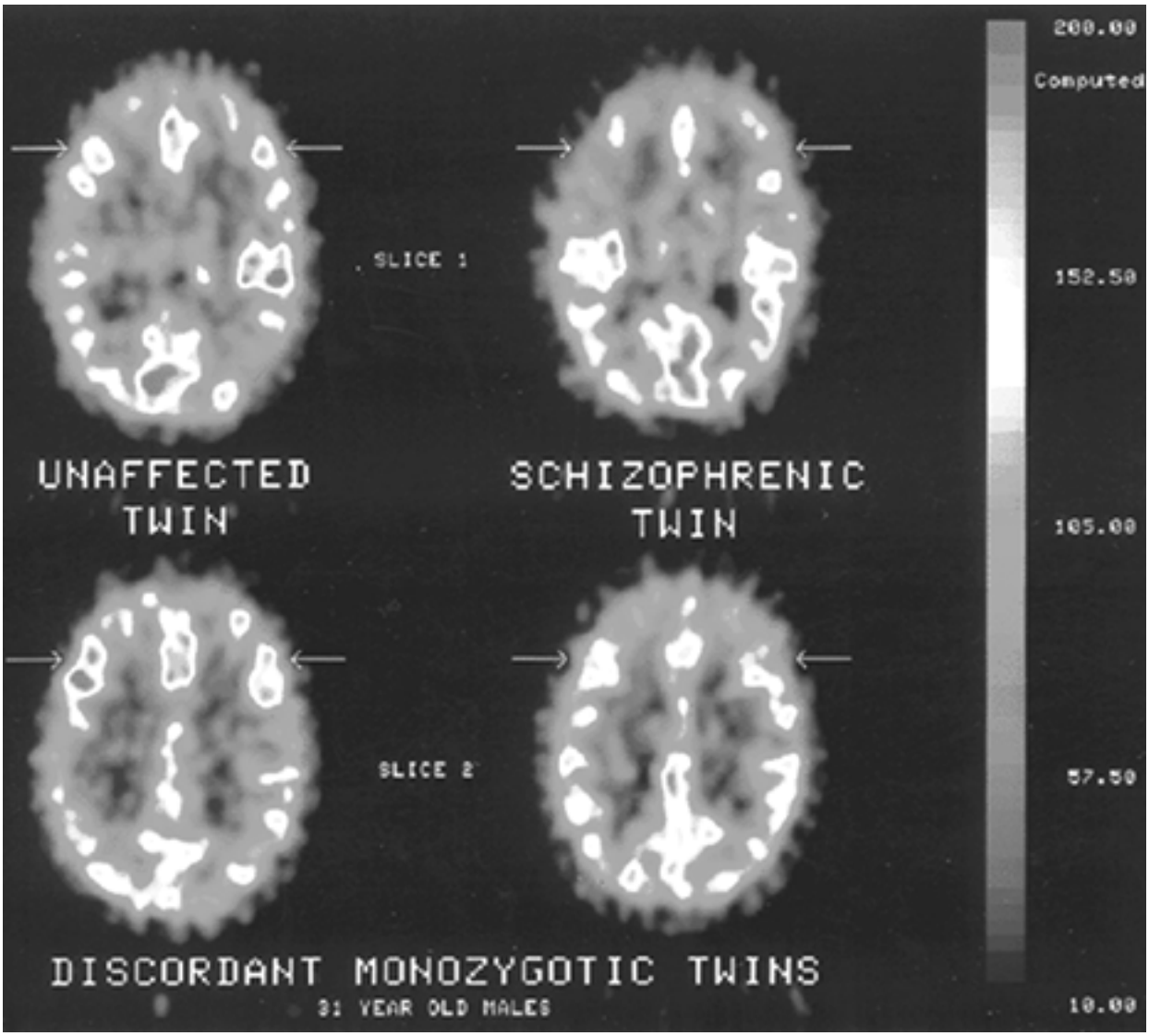

FIGURE 12.4-2 PET scans using H_2O_{15} of two monozygotic twins, one with (right) and one without (left) schizophrenia. Top and bottom scans show two levels through the dorsolateral prefrontal cortex. At the time of scanning, subjects are performing a cognitive task that typically requires prefrontal cortical function. The affected twin blood flow to the dorsolateral prefrontal cortex is markedly reduced compared to the unaffected twin. (Courtesy of R. Berman and D. Weinberger.)(See Color Plate 8.)

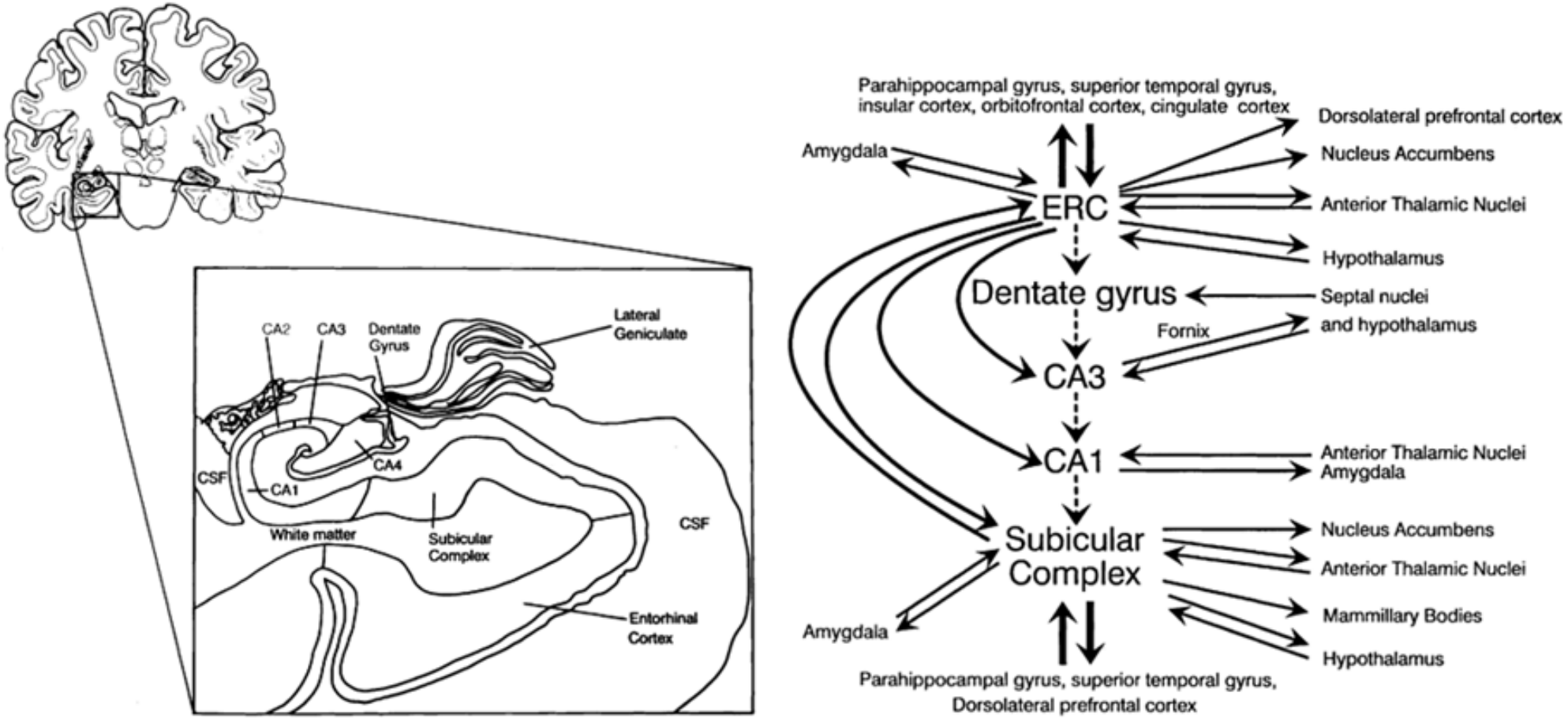

FIGURE 12.4-3 A, Schematic diagram of the mesial temporal lobe at the level of the body of the hippocampus and posterior entorhinal cortex, in coronal section. **B**, The illustrated connections of the coronal section are described in this table. (Drawn by Kyle Christensen.)

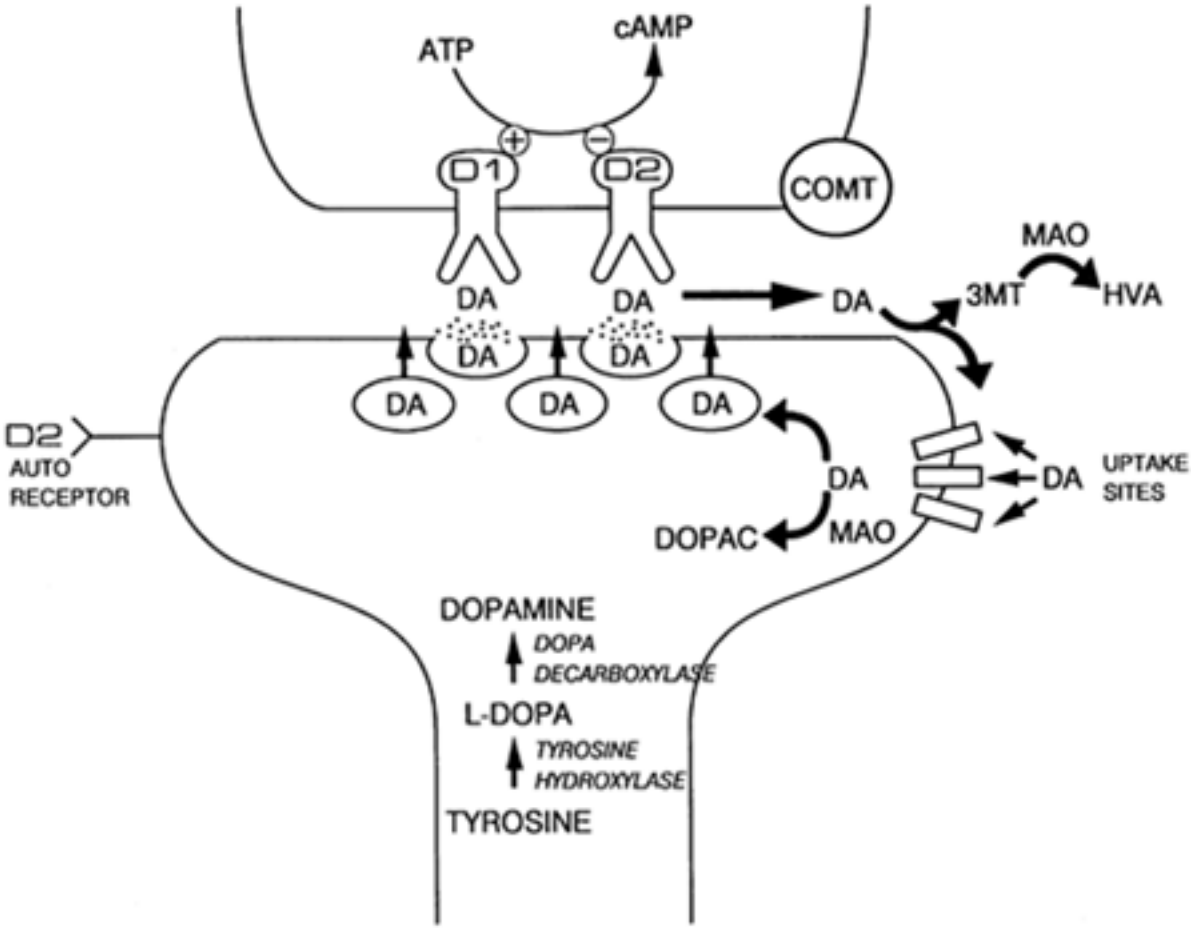

FIGURE 12.4-4 Dopamine metabolism and synaptic structure. In this schematic synapse, dopamine is released into the synaptic cleft where it can act on D_1 or D_2 postsynaptic receptors. Synaptic dopamine is inactivated by reuptake pumps or by catabolism via COMT and MAO. Presynaptic D_2 autoreceptors modulate dopamine synthesis and release in the striatum. (Drawn by Kyle Christensen.)

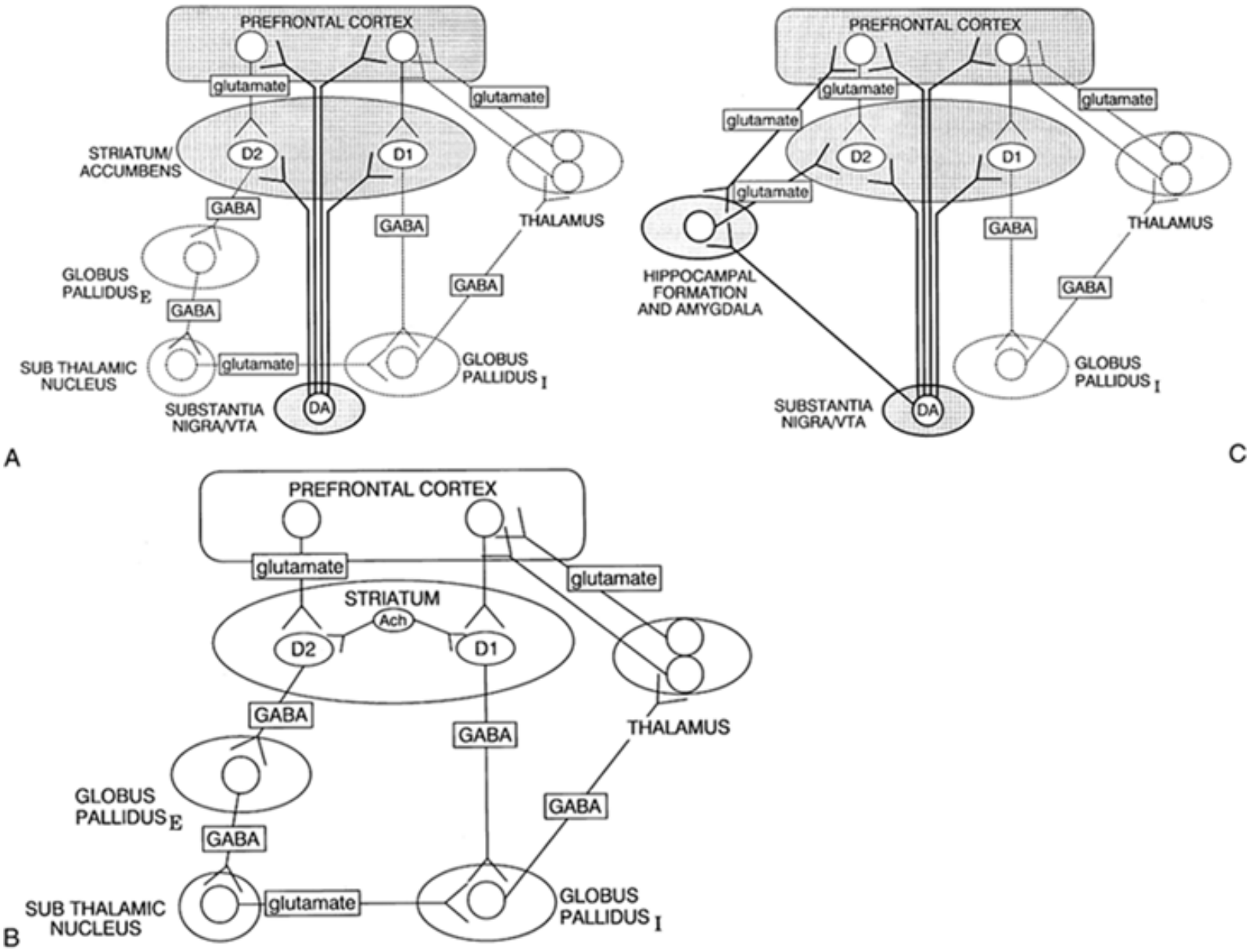

FIGURE 12.4-5 A, Neural networks implicated in the neurobiology of schizophrenia. Cortico-striatal-thalamic pathway. Prefrontal glutamatergic projections synapse on GABAergic striatal neurons that express either D_1 or D_2 receptors. The independent D_1 and D_2 pathways are referred to as the direct and indirect pathways respectively. They have separate efferent pathways projecting to either the globus pallidus, pars externa = E, or pars interna = I. Both pathways ultimately project back to the anterior thalamus. **B**, Ascending dopamine projection pathways modulate circuits in A. Dopamine neurons (DA) from the substantia nigra tend to project mainly to the striatum, while the adjacent ventral tegmental area DA neurons projects primarily to the prefrontal cortex, ventral striatum, and limbic regions. **C**, Limbic projections to circuits from **A** and **B**. The hippocampal formation and amygdala project to the prefrontal cortex and ventral striatum. They receive glutamatergic cortical input and dopamine projections from the VTA. (Drawn by Kyle Christensen.)