Neuroimaging has advanced the study of brain structure and function in schizophrenia. Magnetic resonance imaging provides measures of whole brain and regional anatomy and cerebrospinal fluid volume. Functional methods have included the Xenon-133 technique for measuring cerebral blood flow (CBF); positron emission tomography for assessing metabolism, CBF, and neuroreceptor functioning; and single photon emission computed tomography for studying CBF and neuroreceptors. Despite heterogeneity of patient samples, and studies which differed in the methodologies applied, there is converging evidence implicating three brain systems: frontal, temporolimbic, and basal ganglia. Current emphasis is aimed at probing specific regions across imaging modalities. Now these findings and research paradigms in neuroimaging must be integrated with phenomenological, neurobehavioral, and neuropathological investigations. The application of this technology is already helping to elucidate the neurobiology of schizophrenia, and further important advances can be anticipated.

Neuroimaging methodology has been applied more to the study of schizophrenia than to any other psychiatric disorder. Investigators of brain function in schizophrenia have had to meet the challenge of using developing technology in a complex and heterogeneous disorder. In this article we will first summarize and review major issues and findings in the neurobiology of schizophrenia through the use of neuroimaging, emphasizing the last 5 years. We will then provide an integration across modalities, relating neuroimaging findings to neuropathological and neurobehavioral studies and focusing on brain systems likely to be involved in schizophrenia.

Advances have been made in two related domains of neuroimaging research: structure and function. Structure is examined in neuroanatomic studies, which provide parameters of brain volume. Function is studied in neurophysiologic research, which provides measures of brain energy metabolism (glucose, oxygen) and blood flow; neurochemical research provides information on neuroreceptor density and affinity. Neuroimaging techniques have been able to both inform and advance hypotheses currently influencing schizophrenia research.

Questions of the relation between functional and structural changes and symptom clusters are now easier to address. Dysfunction has been identified in neocortical association areas, temporolimbic regions, and basal ganglia (e.g., Buchsbaum 1990). In retrospect, our initial hypotheses regarding schizophrenia were simplistic. It is unlikely that a disorder as complex as schizophrenia is associated with a single structural or functional lesion in a single neuroanatomical location, and in fact, no such lesion has been identified. However, several findings have emerged consistently, and initial attempts have been made to link...
regional brain abnormalities to behavioral deficits and phenomenology.

**Neuroanatomical Studies: Magnetic Resonance Imaging (MRI)**

Initial studies with MRI have attempted to replicate and extend the research with computed tomography (CT), which showed increased ventricular cerebrospinal fluid (CSF) relative to brain (e.g., Pearlson et al. 1989a). This increase was considered evidence for structural abnormalities due to either developmental aberration or neuronal loss. MRI studies have examined whole brain volume and CSF, particularly in the lateral ventricles (e.g., Kelsoe et al. 1988; Andreasen et al. 1990). MRI has also examined CSF in sulci (Gur et al. 1991) and confirmed a CT finding of increased CSF in sulci (Pfefferbaum et al. 1988).

**Frontal Cortex.** Attention has now turned to the study of specific brain regions implicated in the neurobiology of schizophrenia (Pearlson and Marsh, in press). Few studies of the frontal cortex have been performed in schizophrenia research. Andreasen et al. (1986) and DeMyer et al. (1988) reported globally decreased frontal brain volume or area on midsagittal and axial MRI images. These results, however, have not been replicated (e.g., Smith et al. 1987; Kelsoe et al. 1988; Suddath et al. 1989; Andreasen et al. 1990; Nasrallah et al. 1990; Rossi et al. 1990). Williamson et al. (1991) reported higher left frontal to cortical ratios in schizophrenia associated with negative symptoms. It is too early to draw any firm conclusions from these MRI studies. In part, all prior frontal lobe MRI studies have been limited by the heterogeneity of the region and the difficulty of specifically defining reliable and valid subregions for analysis. For example, meaningful definition of the dorsolateral prefrontal cortex (DLPFC) is critically dependent on the use of surface sulcal gyral patterns. However, these are not apparent from axial or coronal slices. Hence, advanced three-dimensional software using volume images will be necessary to develop appropriate measures of this region for MRI studies.

**Temporal Lobe.** The temporal lobe has also received considerable attention. Reports of abnormalities in schizophrenia implicate both temporal association cortex laterally and temporolimbic structures medially. In lateral temporal lobe, Casanova et al. (1990), using quantitative shape analysis, demonstrated abnormalities of the superior temporal gyrus in MRI scans of patients. Barta et al. (1990) found that schizophrenia patients had smaller volumes of the left anterior superior temporal gyrus (i.e., auditory association cortex), which correlated ($r = 0.70$) with severity of hallucinations, especially auditory. The abnormalities in the superior temporal gyrus were not accounted for by overall brain or temporal lobe volume reduction. These findings were replicated in part in a larger number of patients (Barta et al. 1992) and by other investigators (McCarley et al. 1992c). More recently, two groups reported gray matter volume reductions in the posterior superior temporal gyrus, which on the left side correlated ($r = 0.81$) with the severity of thought disorder (Barta et al. 1992; Shenton et al. 1992b). In addition, left-sided posterior superior temporal gyral gray volume reductions in right-handed schizophrenia patients correlate with amplitude reductions in the P300 components of the auditory event-related potential to novel task-related stimuli (McCarley et al. 1992a, 1992b). Mesial temporal lobe structures such as the hippocampus and amygdala have been implicated in neuropathological studies of schizophrenia (e.g., Bogerts et al. 1985; Arnold et al. 1991), are reported to be reduced in volume on MRI in patients with schizophrenia (e.g., Barta et al. 1990; Bogerts et al. 1990; Suddath et al. 1990), in some instances in first-break patients (e.g., Bogerts et al. 1990).

**Basal Ganglia.** MRI studies in basal ganglia have yielded somewhat inconsistent findings. Several studies of basal ganglia area (e.g., Kelsoe et al. 1988), volume (Persaud et al., in press), and MR T1 relaxation time (Harvey et al. 1991) reported no differences between patients and controls. Jerigan et al. (1991) found increased volume of the lenticular nucleus, that is, the globus pallidus plus putamen. Other investigators have not found changes in lenticular nucleus volume (e.g., DeLisi et al. 1991) or area (Kelsoe et al. 1988). Swayze et al. (1992) reported that male schizophrenia patients have significant enlargement of the putamen and less enlargement in the caudate nuclei.

In addition to the regional volumetric studies under way, there is a need for integration of neuroanatomic data with other major domains including phenomenology, neuropsychology, and functional neuroimaging. Figure 1 illustrates...
Figure 1. Whole brain and regional magnetic resonance imaging

On left: Left lateral view of the three-dimensional volume-rendered brain surface sulcal-gyral anatomy. Rendered image was generated from 1.5 mm coronal spoiled GRASS magnetic resonance images. On right: Three-dimensional volume-rendered view of the superior surface of both temporal lobes using the same data set as the brain on the left. This allows one to see Heschl's gyrus and the planum temporale bilaterally. These images were generated by "dissection" of temporal tissue voxels from the image above the Sylvian fissure. Reprinted with permission from the Division of Psychiatry Neuro-imaging, The Johns Hopkins University, Baltimore, MD

the approach to volumetric MRI studies in schizophrenia research.

Functional Studies: Metabolism and Cerebral Blood Flow (CBF)

Studies of metabolism and blood flow have attempted to address fundamental questions in the study of brain function in schizophrenia. The main imaging techniques applied were the xenon-133, positron emission tomography (PET), and single photon emission computed tomography (SPECT). Investigators have tried to assess whether resting blood flow and glucose metabolism differ between patients with schizophrenia and normal controls.

Another important question is whether clinical variables such as symptoms, chronicity of illness, and pharmacologic intervention are related to these physiologic parameters. Application of neurobehavioral probes during physiologic studies can contribute by linking behavioral performance data with physiologic measures (Gur et al. 1992) and examining the pattern of activated relative to resting parameters in schizophrenia (e.g., Gur et al. 1983, 1985; Weinberger et al. 1986; Berman and Weinberger 1990).

Three major brain dimensions complementing current emphases in the study of brain-behavior relations in schizophrenia have been examined: anterior/posterior, laterality with a focus on the temporal lobe, and subcortical/cortical (Buchsbaum 1990).

Frontal Lobes. The frontal lobes were implicated in early physiologic studies of CBF, which reported that patients with schizophrenia did not show the normal pattern of increased anterior relative to posterior CBF. This "hypofrontal" disturbance in the anterior-posterior gradient has been supported in some (e.g., Mathew et al. 1988; Wolkin et al. 1988; Buchsbaum 1990), but not all (e.g., Gur et al. 1985, 1987a, 1987b; Cleghorn et al. 1989) studies of resting CBF, with the xenon-133 method and glucose metabolism with PET. The relation between this pattern of metabolic activity and clinical variables has been examined. Duration of illness is associated with decreased frontal metabolic activity, with longer duration reported with lower antero-posterior gradient (Wiesel et al. 1987; Mathew and Wilson 1990). Negative symptoms also appear to be related to a decrease in frontal metabolic activity (Volkow et al. 1988). Liddle et al. (1992) found that patients with poor performance on the Stroop test (Stroop 1935), which measures attention, have abnormal CBF in the anterior cingulate cortex. Using SPECT in normals, Rivera-Luna et al. (1991) recently replicated anterior cingulate activation with the Stroop task finding. Of note is that these studies varied not only in the technology applied but also in the definition of regional parameters, with many using ratio of anterior/posterior rather than absolute values of anterior activity.

The work of Weinberger and colleagues (Weinberger et al. 1988;
Berman and Weinberger 1990) supports defective function of the dorsolateral prefrontal cortex in schizophrenia. Subjects executing cognitive tasks that are believed to be dependent on the integrity of the DLPFC showed reduced CBF. In contrast to resting glucose PET studies that sometimes show relative “hypofrontality,” prefrontal flow at rest appears normal in the National Institute of Mental Health studies (Weinberger et al. 1988; Berman and Weinberger 1990) and is only revealed as abnormal in tasks activating DLPFC. Similar activating tasks used by others produce comparable findings (e.g., Kawasaki et al. 1991; Rubin et al. 1991a; Lewis et al. 1992). At least two groups have shown that negative symptoms scores correlate inversely with frontal CBF during performance of executive but not control tasks (Vita et al. 1991; Lewis et al. 1992). The discordant twin schizophrenia study (Berman and Weinberger 1990; Weinberger et al. 1992) reported all affected twins to have reduced DLPFC CBF compared to discordant co-twins.

Temporal Lobe. Functional changes in temporal lobe regions have also been examined. Recent neuroanatomic and neuropsychological studies have shown dysfunction in temporolimbic structures, including the hippocampus, as well as cortical changes (Jernigan et al. 1985; DeLisi et al. 1989). Lateralized abnormalities in these regions, with greater left than right hemispheric dysfunction, are implicated by characteristic clinical features, such as thought disorder, auditory hallucinations, and language disturbances. PET studies of temporal lobe metabolism include findings of both increased and decreased glucose use (Jernigan et al. 1985; DeLisi et al. 1989). Decreased metabolism was also noted in the hippocampus and anterior cingulate cortex (Tamminga et al. 1992). Studies in this area have been limited in part by instrument resolution.

Metabolism and flow pattern in these regions have also been related to symptoms. Liddle et al. (1992) used 18O PET and delineated abnormal CBF in parahippocampal gyrus associated with positive symptoms. Anderson et al. (1991) reported temporal lobe SPECT asymmetries in hallucinating patients. Musalek et al. (1989) reported associations between hallucinations and SPECT flow changes in hippocampus, parahippocampus, and amygdala. There are conflicting reports of superior temporal gyrus functional changes in schizophrenia during active auditory hallucinations. Cleghorn (1990) pointed out that hallucinating schizophrenia patients have significantly lower relative metabolism in Wernicke’s region. McGuire and Murray (1991), using SPECT, reported increased mesial temporal flow associated with auditory hallucinations. Anderson et al. (1991) showed asymmetric temporal lobe perfusion, lower in the left than the right in schizophrenia patients with auditory hallucinations. DeLisi et al. (1989) found greater metabolic activity related to the severity of symptoms in the left anterior temporal lobe. Similarly, Gur et al. (1987b, 1988) reported an association between severity of symptoms and relative increase in left hemispheric activity. Further research is necessary to elucidate the nature and extent of temporal lobe changes in schizophrenia.

Basal Ganglia. Functional changes in the basal ganglia have been examined as neuroimaging has been applied to measure subcortical to cortical relations. Several PET studies implicate basal ganglia dysfunction in schizophrenia (DeLisi et al. 1985; Kling et al. 1986; Buchsbaum et al. 1987; Gur et al. 1987a, 1987b). The withdrawal-retardation factor (emotional withdrawal, blunted affect, and motor retardation) of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962), has been negatively correlated with PET basal ganglia metabolic activity (Wolkin et al. 1985). Neuroleptic-naive schizophrenia patients are reported to have relatively increased blood flow in the left globus pallidus (Early et al. 1989). Other PET studies report decreased basal ganglia metabolism in schizophrenia (Sedvall et al. 1984; Buchsbaum et al. 1987). Some studies found increased basal ganglia metabolic rates following administration of neuroleptic medication (e.g., Buchsbaum et al. 1987). Thus, while PET metabolic and flow studies have added to the evidence implicating basal ganglia involvement in schizophrenia, the exact nature of the dysfunction remains elusive. In particular, basal ganglia-to-frontal lobe relationships in schizophrenia must be explored. Structural/functional imaging has provided evidence of interrelationships between the various key regions. For example, Pearson and colleagues’ preliminary data showed a correlation between MRI volume of superior temporal gyrus and density of dopamine (DA) D2 receptors in caudate/putamen on PET (Pearlson et al. 1991). Work from Rubin et al. (1991b) showed that not only do patients with
schizophrenia fail to activate DLPFC in response to the Wisconsin Card Sorting Test (WCST; Heaton 1981) compared to normal controls, but they also fail to inhibit caudate activation. Hence, in schizophrenia patients, basal ganglia continue to show relatively increased flow in caudate during performance of the task, as opposed to normal controls, who diminish relative flow while increasing perfusion of DLPFC. The study of neuroreceptors provides a direct link for assessing the nature of subcortical abnormalities in schizophrenia. Figure 2 illustrates metabolic images in schizophrenia.

Functional Studies: Neuroreceptors

Evidence suggests that symptoms common in schizophrenia are closely associated with dysfunction of central dopaminergic neurons (Carlsson 1978; Creese 1983; Davis et al. 1991). This dysfunction may represent an excess of DA, either as endogenous DA levels, or density or affinity of D₂ receptors. Much of the impetus for the application of in vivo radiolabeled ligands for human neuroreceptor PET studies (Sedvall et al. 1986) is derived from progress with in vitro binding measurements of receptor density and affinity and of neuroreceptor autoradiography. PET studies first focused on D₂ receptor because of its clinical relevance and potential to discriminate illness from treatment effects such as receptor induction. Two quantitative PET methodologies evolved to measure D₂ receptors (Wong et al. 1986a, 1986b, 1986c; Farde et al. 1990; Sedvall 1990). Initial reports from Karolinska Hospital, Sweden, and the Johns Hopkins Hospital, Baltimore, Maryland, on drug-naive patients disagreed. Wong et al. (1986c) found that schizophrenia patients had dopamine D₂ Bₘₐₓ values two to three times those of age-matched normal controls. By contrast, Farde et al. (1990) reported that both Bₘₐₓ and Kᵣ values were almost identical in patients and controls. Asymmetry, with left putamen Bₘₐₓ values significantly higher than right in schizophrenia patients only, was noted in the Karolinska data (Farde et al. 1990).

These striking differences could be due to dissimilarities in PET measurement methods and in the subject populations (Andreasen et al. 1988). The Swedish group used (¹¹C) raclopride, a highly specific and moderately avid substituted benzamide compound, as a D₂ receptor ligand. Raclopride reaches equilibrium with the D₂ receptor during the time of the scan. By using several different specific activities of ligand per subject, one obtains equilibrium binding data, an in vivo analog of the in vitro Scatchard plot. An advantage of this approach is its conceptual simplicity. Radiation dose constraints usually limit the number of scans per subject to two, which is adequate but perhaps fewer than optimal.

The Hopkins approach employs the less D₂-specific, more avidly bound ligand (¹¹C)-N-methylspiperone (NMSP), which does not achieve equilibrium. The time–activity ratio continues to increase linearly during the imaging period due to persistent binding of the ligand at the D₂ site. This approach assesses radioligand D₂ receptor binding using a dynamic four-compartment kinetic model. Binding kinetics are compared before and after administration of haloperidol, which competes with the NMSP for binding at the D₂ site. The mathematical procedure to calculate Bₘₐₓ is also more...
complex than with the Karolinska method.

Several recent reports accentuate differences between properties of the two ligands. Seeman and Niznik (1990) noted that raclopride binding may be sensitive to displacement by endogenous DA and thus may underestimate elevated D₂ receptors. This is especially relevant because, as noted above, endogenous DA levels as well as receptor characteristics may differ between schizophrenia patients and normals. With NMSP, internalization or endocytosis of ligand-receptor complexes has been reported by Chugani et al. (1988). Hall et al. (1990) compared in vivo binding properties of raclopride versus NMSP and reported differences between the ligands, a finding that is compatible with part of the D₂ site being occupied only by NMSP. Either of these phenomena may account for the two ligands assessing related but nonidentical aspects of the D₂ receptor.

Lidow et al. (1991) used autoradiographic techniques to compare radiolabeled raclopride versus spiperone distribution in the nonhuman primate cerebral cortex. The two radioligands showed marked distribution differences, with spiperone tending to label serotonin (5HT)-1C and alpha-2 adrenergic sites as well as D₂ receptors in prefrontal cortex. Raclopride appeared to provide more specific estimation of D₂ receptor distribution than spiperone. Much work is still needed to develop and validate models for receptor measurement (Reiman and Mintun 1990).

There were also potentially important differences in the populations examined in age and length of illness, with Hopkins patients being older and ill longer. However, decline in D₂ receptors with age (e.g., Wong et al. 1984) should have obscured patient and control differences in the Hopkins group and highlighted such differences for the Karolinska investigators.

Martinot et al. (1990), using Br-76 bromospiperone PET, showed no patient control differences in untreated schizophrenia. The Martinot method, like the initial Wong et al. ratio approach (1985), uses a method that may be sensitive to blood flow limitations. Recently, Tune (1992) replicated the initial report in a new sample of drug-naive schizophrenia patients. Other data reveal D₂ density increases in psychotic but not nonpsychotic bipolar patients. The degree of increase is comparable to that reported in schizophrenia (Wong et al. 1985; Pearlson et al. 1989b). This raises questions regarding the specificity of the DA hypothesis to schizophrenia versus other psychotic syndromes.

Postmortem studies support D₂ receptor increases in schizophrenia. Seeman and Niznik (1990) examined D₁ and D₂ receptors and DA transporter sites (DTS) in postmortem tissue. The D₁ and DTS densities in schizophrenia patients were no different from those of normals. However, D₂ receptor densities in caudate and putamen of schizophrenia patients were significantly elevated, including cases never treated with neuroleptics. The investigators also report some preliminary evidence of changed D₂ receptor structure in schizophrenia patients and possible uncoupling of links between D₃ and D₂ receptors (Seeman et al. 1989).

In addition to contributing to the above studies, the Karolinska group has clarified clinically relevant neuroleptic mechanisms by examining drug actions on both D₁ and D₂ receptors (Farde et al. 1988; Sedvall 1990). In vivo D₂ receptor blockade was assessed by percentage reduction in specific (¹³C) raclopride binding and D₁ receptor occupancy measured with (¹¹C) SCH 23390. Clinical doses of 11 pharmacologically distinct classes of neuroleptics led to significant (70%–89%) dose-dependent D₂ receptor blockade, which occurred within several hours of drug administration. Receptors remained blocked for hours and occupancy declined predictably from the established pharmacological half-life of a given drug. The time course thus revealed for D₂ receptor blockade is significantly shorter than that for the clinical resolution of psychotic symptoms following neuroleptic administration. Furthermore, positive symptoms of schizophrenia relapse significantly later than D₂ receptors become unoccupied following drug discontinuation (Sedvall et al. 1986; Farde et al. 1988; Sedvall 1990). Wolkin et al. (1989) demonstrated that neuroleptic-resistant schizophrenia patients were no different in degree of D₂ receptor occupancy by neuroleptic than neuroleptic responders. Kessler et al. (1991) have used epidepride, a potent D₂ receptor antagonist, to explore extrastriatal D₂ receptors in autoradiographic and in vivo neuroimaging studies. Iodine-labeled epidepride may prove to be a useful SPECT agent for exploration of D₂ sites since the agent labels relevant receptors in prefrontal and cingulate cortex as well as in striatum. The specific D₂ receptor SPECT ligand 3-iodobenzamide has become available (Kung et al. 1988) and is being used to study DA D₂ receptors in patients with schizophrenia (Brucke et al. 1988;
Konig et al. 1991).
Thus, while these experiments confirm and extend hypotheses of neuroleptic action, important questions remain unanswered. Figure 3 illustrates neuroreceptor findings in schizophrenia.

In a recent summary of the status of PET studies in schizophrenia, Sedvall (1992) focused on two areas: regional brain energy metabolism and neuroreceptor studies. He concluded that the most important factors for understanding the pathophysiology of schizophrenia will be advanced resolution and development of new ligands for neurotransmitter systems. While we agree on the potential of this area of PET and SPECT, we believe that metabolic studies also have great potential (Gur and Gur 1992). When neuroimaging studies are placed in the context of neuropsychiatry's overall effort to establish neural substrates for schizophrenia, it is clear that they have contributed and will continue to advance the understanding of brain dysfunction's relationship to behavior. The field has reached some maturity in establishing paradigms, and the current need is for adequate sample size in patient and normal populations with attention to variability in brain function in relation to individual differences, gender, and age. Two types of probes can enhance our understanding of brain function in schizophrenia. The first is the application of tracers for measuring neuroreceptor systems as described by Sedvall (Sedvall et al. 1986), which is the way to proceed for neuropharmacologic studies. The second is neurobehavioral probes (Gur et al. 1992), which are probably best suited to metabolic studies. Neurobehavioral probes are challenge tasks presented to subjects while the metabolic study is being performed. While there are a number of reports where 18-fluorodeoxyglucose studies were performed during cognitive activation (Gur et al. 1983; Volkow et al. 1987; Buchsbaum 1990), a better ligand for such studies is 15O-labeled water for measuring CBF. The reason is that the short half-life of the ligand permits repeated measures under different task conditions, which strengthens the design by eliminating sampling error and allowing the demonstration of the specificity of task effects. Studies with other physiologic neuroimaging methods, such as the xenon-133 clearance technique, have used this approach successfully in the study of schizophrenia (Gur et al. 1983, 1985; Weinberger et al. 1986; Berman and Weinberger 1990). This has not been done in PET and requires consideration of several factors: task appropriateness for the PET environment; task difficulty, validity, and reliability of tasks in relation to the concepts they measure; specificity of effect for task and population; and availability of performance data that can be correlated with metabolism.

One of the major challenges in this research is the integration of neuroimaging data across anatomic and functional measures with clinical and neurobehavioral variables. The main technical difficulty is in finding means of cross registration of data within brain topography. A major methodological task relates to the consistent finding that each set of data is highly intercorrelated within itself, and therefore it is difficult to isolate relationships across domains (Warach et al. 1992).

**Figure 3. Neuroreceptor function in schizophrenia**

Tranaxial positron emission tomography images through basal ganglia using the ligand 11C N-methylspiperone to display dopamine D2 receptors in a never-medicated patient with late-onset of schizophrenia (paraphrenia). Left image shows uptake in the unblocked state, showing high basal ganglia uptake relative to cortex. Right image is of a second scan taken several hours after pretreatment with unlabeled oral haloperidol. D2 receptors are blocked by the cold ligand with consequently lower basal ganglia activity. Photograph is courtesy of Dr. Dean Wong, Department of Radiology, The Johns Hopkins University, Baltimore, MD.

**Toward Integration of Neuroimaging With Neurobiology**

Structural and functional studies in schizophrenia suggest that several brain regions are affected. Convergent research implicates specific
regions. Several lines of evidence imply that the frontal cortical area, in particular the DLPFC, is dysfunctional in schizophrenia. Abnormalities affecting this region seem linked to impaired motivation, socialization, and complex problem solving. Neuropsychological deficits in schizophrenia also suggest frontal lobe involvement (Stuss and Benson 1984; Goldberg et al. 1990). Anatomy of the DLPFC in nonhuman primates, extensively researched by Goldman-Rakic and collaborators (Goldman-Rakic 1987, 1990) indicates multiple links to other association cortical areas and to basal ganglia.

The temporal lobe is also implicated in schizophrenia (Crow 1990). Kraepelin suggested the temporal cortex as a pathological locus for auditory hallucinations and thought disorder on the basis of neural representations of auditory and language functions. The superior temporal gyrus (STG) is implicated by several findings: (1) direct electrical stimulation of this structure in conscious individuals was virtually the only site from which Penfield and Perot (1963) elicited hallucinatory phenomena; (2) the P300 evoked-potential wave, provoked by novel auditory stimuli, is believed to be generated in the vicinity of STG (Johnson 1988), and P300 amplitude is consistently reported as reduced in patients with schizophrenia; (3) the Sylvian fissure overlies STG and expands in cases of gyral atrophy or hypoplasia—neuroimaging studies report Sylvian fissure atrophy, more marked on the left side in schizophrenia, in association with both reduced P300 amplitude and positive symptoms, particularly hallucinations (McCarley et al. 1989); (4) magnetoencephalographic work in schizophrenia (Reite et al. 1989) is consistent with left-sided disturbances originating from the STG region; and (5) STG volume is decreased in schizophrenia, on the left side anteriorly correlating with hallucinations (Barta et al. 1990) and posteriorly with thought disorder (Shenton et al. 1992b) and P300 amplitude reduction (Shenton et al. 1992a).

Evidence for temporolimbic circuit involvement in schizophrenia is strong. Primacy of temporolimbic dysfunction is suggested by the occurrence of positive symptoms following damage to this area and their appearance in some cases of temporal lobe epilepsy (Flor-Henry 1969). Neuroanatomically, the area connects reciprocally to the DLPFC (Goldman-Rakic 1990). Functions localized to this region may be relevant in disorders of language, memory, drive, and emotions in schizophrenia, leading Roberts (1991) to propose that primary damage in schizophrenia to mesial temporal structures, including entorhinal cortex, plays a "crucial role in integration and processing of output from association cortex" (p. 209). The well-replicated memory deficits of schizophrenia (e.g., Neale and Oltmanns 1980; Calev 1984; Saykin et al. 1991) may be a consequence of limbic-diencephalic pathology. These brain areas share major connections to prefrontal areas through the medial dorsal thalamus. The entorhinal cortex may be viewed as a portal through which neocortical information reaches hippocampus and thereafter other structures within the limbic system. Hence, multimodal sensory representations are funneled into "a meeting point for internal and affective data with current and past sensory information" (Trimble 1991, p. 61). Roberts (1990, 1991) also notes that information from association cortices converges on the entorhinal cortex, with the parahippocampal gyrus and subiculum of the hippocampus "gating" information entering and leaving the hippocampus. Hence, dysfunction in the parahippocampal gyrus could secondarily exert significant effects on higher order integrative cortical systems, including dorso-lateral prefrontal cortex, auditory association cortex, and posterior parietal cortex. Similarly, Arnold et al. (1991, 1992) argue that entorhinal cortex is pivotal for neural systems mediating corticohippocampal interactions.

Among the key regions reviewed earlier, the basal ganglia have the most behaviorally relevant functions, due in part to their diverse afferent projections from all cortical areas and extensive frontal lobe efferents passing through the thalamus (Alexander and Crutcher 1990). The most relevant circuits for schizophrenia are the oculomotor circuit focused on frontal eye fields, the prefrontal circuit focused on DLPFC, and the limbic circuit projecting to the anterior cingulate and medial orbitofrontal cortex. Stevens (1991) has suggested a striatal origin for symptoms of schizophrenia, and DA-rich nuclei, such as the caudate, participate in regulation of attention (DeLong 1972; Mesulam 1981). Deficits on vigilance tasks are major features of schizophrenia (Nuechterlein and Dawson 1984). The core neurobehavioral deficit of attentional disturbances likely reflects the interaction of prefrontal and subcortical DA systems (Seidman 1983; Stuss and Benson 1984). Although an anatomically specific attentional mechanism is not known, the relationship between smooth pursuit eye movement per-
formance and attention is also pertinent. However, clear evidence for primary basal ganglia involvement in the pathogenesis of schizophrenia is still lacking.

Although the precipitating event in schizophrenia remains obscure, new neuropathological methods using molecular probes may shed some light. The neuropathological findings (Benes et al. 1986; Benes and Bird 1987; Roberts 1990; Arnold et al. 1991; Bogerts et al. 1991) indicate that schizophrenia is acquired in late fetal development or in the perinatal period. These findings also indicate that the characteristics are caused by hypodysplasia, not atrophy. Of brain structures vulnerable to perinatal complications, the hippocampus and pallidum are especially susceptible to early hypoxia or infection, suggesting pathologic etiology (Lyon et al. 1989). Although MRIs performed by Wood and Flowers (1990) demonstrated some evidence of progressive ventricular enlargement in some schizophrenia patients, longitudinal MRI studies performed 1 to 2 years after the onset of schizophrenic symptoms (Degre et al. 1991; De Lisi et al. 1992) do not show striking increases in ventricular size as the illness evolves. Weinberger (1987) has argued that static damage occurring early in development could still manifest as a clinical syndrome that characteristically appears in adolescence and has a waxing and waning course.

Extensive reciprocal connections between the circuits mentioned above were shown with other regions identified in human studies as being involved in the pathophysiology of schizophrenia (e.g., Goldman-Rakic 1987, 1990). These include superior temporal gyrus, parahippocampal gyrus, anterior and posterior cingulate cortex and entorhinal cortex, hippocampus, amygdala, and caudate. The heteromodal association cortical circuit that subserves higher-order cortical functions—which we have argued elsewhere may be especially disordered abnormalities in schizophrenia (Pearson and Petty, in press)—has extensive links with both the temporal limbic and the basal ganglia circuits.

Crow (1990) suggested one specific site of involvement, the planum temporale, in the distributed neural network that constitutes the heteromodal association cortical loop. In part, Crow’s hypothesis stems from reports of lateralized abnormalities in schizophrenia (e.g., Flor-Henry 1969; Gur 1978). This is another area where imaging and neurobehavioral data show some convergence (Gur et al. 1983, 1985, 1987a, 1987b, 1989). Bogerts et al. (1990) found left-sided temporal lobe abnormalities to be more pronounced in male schizophrenia patients. Although both male and female patients had increased anterior temporal horn volume, males also had significantly increased left posterior amygdala-hippocampal as well as temporal horn volumes. Suddath et al. (1990) demonstrated that in monozygotic twins discordant for schizophrenia the ill co-twins had decreased left temporal lobe gray matter volume and bilateral hippocampal area. Such differences were not seen in normal pairs of monozygotic twins. Bracha (1991) cites evidence that the normal brain develops asymmetrically, with right-sided temporal lobe structures developing significantly ahead of their homologs on the left. Hence, developmental disruptions at crucial times (e.g., in the second trimester of gestation) will follow relative maturation of some right-sided structures but precede full development of corresponding left-sided structures. Such disruptions will result in apparent unilateral involvement of left-sided temporal lobe structures. This explanation conceptualizes lateralized findings as an epiphenomenon of the normal developmental sequence.

By contrast, Crow’s hypothesis emphasizes associations between schizophrenia and disturbances in the expression of the gene that controls normal cerebral asymmetries, especially those that are expressed most obviously in the planum temporale. The planum temporale lies directly beneath a posterior portion of the superior temporal gyrus and represents Wernicke’s area. Petrides and Pandya (1984) elucidated projections from this locale to specific matching regions within frontal lobe association areas.

Crow’s hypothesis derives from several sources: (1) males have an earlier onset of schizophrenia; (2) cerebral asymmetry is a relatively late development in primate evolution, one linked with both handedness and the human capacity for speech and communication; and (3) major asymmetries in humans are normally obvious in the region of the planum temporale and more marked in males. Crow hypothesizes that the same gene controls psychosis and human handedness. Thus, genetically determined anomalies in the development of the planum temporale are responsible both for local morphologic abnormalities and are linked with thought disorder in schizophrenia and with the frequent anomalous hand dominance observed in schizophrenia (Gur 1977). The planum temporale is linked through the superior temporal gyrus to auditory hallucinations,
thought disorder, and P300 abnormalities in schizophrenia. This connection can be tested with MRI (Steinmetz et al. 1990).

Goldman-Rakic’s work (1987) shows that the superior temporal gyrus forms a link between temporal limbic structures and heteromodal association cortex, in particular DLPFC. DLPFC itself is unlikely to be the site of the primary lesion in schizophrenia. Although the DLPFC is functionally abnormal when stressed, as shown by Weinberger (1987, 1991), there has been no clear demonstration of either neuropathological abnormalities or structural MRI changes in this region. In fact, as recently pointed out by Weinberger (1991), failure of the DLPFC to engage metabolically or in terms of relative regional cerebral blood flow (rCBF) in patients with schizophrenia when performing the WCST is “suggestive of a defect in functional connectivity, not a primary lesion” in this area. Furthermore, this “behavior involves a recruitment of specific neural networks” (p. 509). The WCST involves a network including hippocampus, DLPFC, and parietal lobe. Since the planum temporale, DLPFC, and inferior parietal lobe constitute a heteromodal association cortical loop, Pearlson and Petty (in press) have proposed that disturbances in this loop are a primary substrate of the schizophrenic syndrome. Bilder et al. (1991) have shown links between hippocampal volume reductions on MRI and decreased performance on the WCST.

The extent to which abnormalities in the above circuits relate to clinical features in schizophrenia is an important issue. Liddle and coworkers (1992) analyzed correlation patterns between schizophrenic symptoms and developed three syndromes: psychomotor poverty (flat affect, poverty of speech, decreased spontaneous movement); disorganization, characterized by formal thought disorder and inappropriate affect; and reality distortion (delusions and hallucinations). They proposed that the psychomotor poverty syndrome was associated with dysfunction of left DLPFC, disorganization syndrome with dysfunction of the right ventral prefrontal cortex, and reality distortion syndrome with medial temporal lobe abnormalities. Liddle et al. (1992) assessed CBF using a steady-state 15O PET technique. This study tended to confirm the original hypotheses that psychomotor poverty would be associated with relatively reduced CBF in the left DLPFC and also with hyperperfusion of the head of the caudate nucleus. Right ventral prefrontal cortex was relatively hypoperfused in the disorganization syndrome, which was positively correlated with CBF in right medial prefrontal cortex and anterior cingulate. Broca’s area was relatively hypoperfused, a finding that agrees with Cleghorn et al.’s (1989) data. Decreased CBF was also found in the angular gyrus. For the reality distortion syndrome score, the most significant correlation was positive with left parahippocampal gyril CBF.

By studying a series of key functional, structural, and clinical measures within the same patient population, a more comprehensive systemwide picture of the disease is likely to emerge. The field is now poised to conduct this integrated research, which is likely to advance understanding of schizophrenia’s neural basis.

Summary and Future Directions

Structural and functional findings emerging from neuroimaging studies in schizophrenia have begun to provide a bridge linking basic and clinical behavioral sciences. Findings such as hypofrontality or D_2 receptor increases in PET studies have been shown to be more complex than initially thought. The relationship between structural and functional changes in the brains of patients with schizophrenia also requires elucidation. From the viewpoint of specificity, functional changes initially hypothesized to be specific to schizophrenia, such as reduced relative frontal glucose metabolism or dopamine receptor abnormalities, and structural changes, such as increased CSF and reduced temporal lobe volume, are also reported to occur in affective disorders.

We are now equipped to examine hypotheses that address fundamental questions on brain-behavior relations in schizophrenia: (1) What initiates the pathophysiological process ultimately manifested as schizophrenia? (2) When does the process occur in terms of neurodevelopmental versus neurodegenerative processes and their timing? (3) In what region does the process first occur? (4) Which areas are then affected secondarily? (5) How do these changes develop? (6) How do these abnormalities relate to the clinical syndrome of schizophrenia? Finally, (7) Are the processes consistent across schizophrenia subtypes? The commitment and excitement of students of schizophrenia should be accompanied with responsibility and care as these lines of investigation are pursued.
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