Schizophrenia Research: A Biennium of Progress
Proceedings From the Sixth International Congress on Schizophrenia Research
Colorado Springs, CO, April 12–16, 1997

by Robert W. Buchanan, Peter F. Buckley, Carol A. Tamminga, and S. Charles Schulz

Abstract

The Sixth International Congress on Schizophrenia Research (ICOSR) took place in Colorado Springs, Colorado, April 12–16, 1997, where over 1,000 scientists presented and listened to the latest developments in the search for the cause and treatment of schizophrenia. The ICOSR is sponsored by Maryland Psychiatric Research Center, Case Western Reserve University, and the William K. Warren Foundation. The National Institute of Mental Health and several pharmaceutical companies contributed generously to the meeting. The ICOSR is co-organized by Dr. Carol A. Tamminga, Maryland Psychiatric Research Center, University of Maryland at Baltimore, and Dr. S. Charles Schulz, Case Western Reserve University, Cleveland, Ohio. The William K. Warren Research Award is given to a senior investigator, who has made outstanding contributions to our understanding of schizophrenia. The fifth William K. Warren Research Award was presented to Dr. Philip S. Holzman in recognition of his contributions to the identification of eye-tracking abnormalities as a potential phenotypic marker of the illness and also in recognition of his work as a lifelong mentor for schizophrenia researchers. The ICOSR Young Investigator Awards are presented to junior investigators who have demonstrated the potential to make significant contributions to research on schizophrenia. These awards promote scientific development by enabling these young researchers to attend the meeting. There were 30 Young Investigator Award winners. The ICOSR meeting is organized into four sessions: (1) a morning plenary session; (2) a plenary lecture; (3) a poster session; and (4) concurrent afternoon oral sessions. The morning plenary sessions are comprised of a set of 30-minute lectures, which provide an overview of a particular topic area relevant to schizophrenia research. The plenary lecture is an invited lecture on a basic topic related to current research efforts in schizophrenia. The poster sessions provide a forum for the presentation of prepublication reports of basic and clinical science projects. The afternoon sessions are a collection of approximately 10 focused presentations on current research projects related to a specific topic area. The purpose of this report is to provide an account of the proceedings from the plenary and afternoon oral sessions.

Key words: Animal models, genetics, antipsychotics, cognitive neuroscience.


The International Congress on Schizophrenia Research (ICOSR) is a biannual meeting designed to bring together investigators from diverse disciplines, both clinical and basic science, and provide a setting that encourages the sharing of scientific data and ideas and the development of collaborations. Over 1,000 investigators from around the world congregated in Colorado Springs, Colorado, to present and listen to the latest developments in the search for the cause and treatment of schizophrenia. The ICOSR is sponsored by Maryland Psychiatric Research Center, Case Western Reserve University, and the William K. Warren Foundation. Both the National Institute of Mental Health and several pharmaceutical companies contributed generously to the meeting. The ICOSR is co-organized by Dr. Carol A. Tamminga, Maryland Psychiatric Research Center, University of Maryland at Baltimore, and Dr. S. Charles Schulz, Case Western Reserve University, Cleveland, Ohio. The coordinator is Susan Nusbaum (Maryland Psychiatric Research Center). The Program Planning Committee, chaired by Dr. Jeffrey Lieberman, University of North Carolina, Chapel Hill, and program consultants put together a dynamic program

Reprint requests should be sent to Dr. R.W. Buchanan, Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228.
schedule that integrated basic science underpinnings with the clinical application of state-of-the-art approaches to understanding the brain, specifically, how disturbances in normal brain function can lead to schizophrenia, and the translation of this knowledge into the development of new and better treatments.

The ICOSR also acknowledges the contributions of established investigators and encourages the talent and development of young investigators. The William K. Warren Research Award is given to a senior investigator who has made outstanding contributions to our understanding of schizophrenia. The fifth William K. Warren Research Award was presented to Dr. Philip S. Holzman in recognition of his contributions to the identification of eye-tracking abnormalities as a potential phenotypic marker of the illness and also in recognition of his work as a lifelong mentor of schizophrenia researchers. The ICOSR Young Investigator Awards are presented to junior investigators who have demonstrated the potential to make significant contributions to research on schizophrenia. The awards promote scientific development by enabling these young researchers to attend the meeting. The Young Investigator Awards are supported, in part, by the National Institute of Mental Health, Rockville, Maryland. There were 30 Young Investigator Award winners. Most of these young investigators played an active role in reviewing the presentations discussed in this report.

The ICOSR meeting is organized into four sessions: (1) a morning plenary session, (2) a plenary lecture, (3) a poster session, and (4) concurrent afternoon oral sessions. The morning plenary sessions comprise a set of 30-minute lectures that provide an overview of a particular topic area relevant to schizophrenia research. The plenary lecture is an invited lecture on a basic topic related to current research efforts in schizophrenia. The plenary lecturers were Drs. Douglas O. Frost, Eric I. Knudsen, and Stephen M. Kosslyn. The poster sessions provide a forum for the presentation of prepublication reports of basic and clinical science projects. The afternoon sessions are a collection of approximately 10 focused presentations on current research projects related to a specific topic area.

The purpose of this report is to provide an account of the proceedings from the plenary and afternoon oral sessions. We are not providing a comprehensive review of the poster sessions. We will attempt to highlight reports that are of particular interest or importance for understanding the current major directions of schizophrenia research. Only the first author of each report is cited. Abstracts of the afternoon and poster presentations are presented in a special issue of Schizophrenia Research (volumes 1, 2, 1997). We have based our review on our observations and notes of presentations and have confirmed details, to the extent possible, through correspondence with the presenting authors. The occurrence of concurrent afternoon sessions precludes an exhaustive or inclusive discussion of the proceedings.

Animal Models of Schizophrenia

The development of informative animal models of schizophrenia has been complicated by the uniquely human nature of the illness. The central role that language and thought play in the manifestations and diagnosis of the disorder and the diversity of illness manifestations have precluded the development of a comprehensive animal model of schizophrenia. A more fruitful approach has been to develop models for specific aspects of the illness. In a plenary session, Drs. John Crabbe and Marc Caron presented two approaches for developing animal models relevant to the study of complex behaviors. Dr. Crabbe discussed the use of quantitative trait loci to examine the relationship between a target trait and specific chromosome regions putatively containing a gene or genes affecting the target trait. The use of this approach to examine chromosome regions related to alcohol consumption in mice was presented. Dr. Caron discussed the use of animals who have the function of a single gene eliminated (knockout animals) for examining the effect of specific proteins on behavior. He presented data on dopamine (DA) transporter knockout mice. The DA transporter appears to be the most potent regulator of synaptic DA levels in the basal ganglia and other regions receiving DA input. The characterization of DA transporter knockout mice allows for a greater understanding of the physiological effects of DA.

The earliest descriptions of schizophrenia by Kraepelin (1919) and Bleuler (1919/1950) noted the attentional impairments in patients with schizophrenia. These observations have been supplemented by more than 30 years of research on attention and information-processing impairments in schizophrenia. Current studies have led to the proposition that patients with schizophrenia have a primary impairment in the gating of sensory information. An animal model for this aspect of schizophrenia is the prepulse inhibition (PPI)/startle response model developed by Dr. Mark Geyer and colleagues. The neuroanatomy and much of the neurochemistry of PPI has been delineated in animals, and the behavioral phenomenon can be elicited in both animals and humans. Of particular interest is the use of the model to examine the effect of antipsychotics on PPI, including both direct effects and the ability of these agents to block the actions of pharmacological agents, which in turn modulate neurotransmitter systems that may be involved in the patho-
physiology of schizophrenia. For example, ketamine and phencyclidine both disrupt normal PPI; this effect is blocked by clozapine, olanzapine, and quetiapine, but not haloperidol and, perhaps, not risperidone. The differential blocking effect of these antipsychotic agents may have important implications for understanding their effects on cognitive functioning in patients with schizophrenia.

Neurodevelopmental hypotheses are the dominant pathogenic hypotheses guiding current research efforts. The relationship of various perinatal insults to increased risk for schizophrenia, and the presence of cognitive, neurological, and social impairments in a substantial proportion of children who go on to develop schizophrenia provide indirect support for such hypotheses. Dr. Daniel Weinberger and colleagues have examined two models designed to explain the putative neurodevelopmental origin of schizophrenia. The first model uses the excitatory amino acid, ibotenic acid, to create lesions of the ventral hippocampal cortex in neonatal and adult rats. The second model uses surgical lesions of the temporal cortex in neonatal and adult monkeys. In a series of experiments, they have observed that neonatal hippocampal lesions produce behaviors or impairments—sometimes analogous to what is observed in patients with schizophrenia (e.g., altered PPI and delayed alternation task performance)—that become manifest with age and are not observed in adult lesioned animals. The effect of neonatal lesions are also neuroanatomically specific, with neonatal cortical lesions failing to produce the delayed onset of behavioral abnormalities. In recent studies using magnetic resonance spectroscopy, neonatally lesioned monkeys have been shown to exhibit a selective reduction of N-acetylaspartate (a putative marker of neuronal integrity) in the dorsolateral prefrontal cortex. These studies support the central role of the hippocampus in the neurodevelopmental origin of schizophrenia, a role that is reinforced by the particular sensitivity of the hippocampus to a number of the putative perinatal risk factors for schizophrenia.

Extrapyramidal symptoms (EPS) are a major side effect of conventional antipsychotics and are a major impetus behind the development of so-called atypical antipsychotics. These new drugs are designed to exhibit minimal EPS within the dosage range used to treat positive symptoms. Animal models can be used to evaluate the acute and chronic EPS effects of antipsychotics and to ascertain which agents are effective in reversing EPS. Dr. Daniel Casey has developed a cebus monkey model that evaluates the relationship between the dosage ranges that produce antipsychotic and dystonic effects. In this model, there is extensive overlap in the antipsychotic and dystonia-inducing dosages of haloperidol, whereas there is a relatively wide separation of these dosages for chlorpromazine. If these two drugs are used as the opposite ends of a continuum, then one can compare how the atypical drugs fare. Risperidone shows a pattern similar to that of haloperidol, whereas olanzapine, quetiapine, and sertindole are more similar to chlorpromazine. Clozapine is the only drug that has not been shown, at any dose, to cause a dystonic reaction.

The plenary session on animal models was complemented by two of the plenary lectures. Dr. Frost discussed compensatory mechanisms affecting the impact of neurodevelopmental lesions on neural circuit connectivity. These mechanisms may limit the adverse impact of even relatively large lesions. Dr. Knudsen presented data from his work examining the neural circuitry underlying the ability of the barn owl to detect auditory stimuli. In lesioned or otherwise altered animals, the normal circuitry is rewired to compensate for the alteration, with the neural rewiring mediated by the glutamatergic/N-methyl-D-aspartate (NMDA) system. These studies have potentially profound implications for our understanding the structural and functional neuroanatomy of schizophrenia, especially in light of the predominance of neurodevelopmental hypotheses. They suggest that the differential metabolic patterns observed in functional imaging studies may reflect the reorganization of the brain in schizophrenia to compensate for an early developmental insult and not necessarily the failure to activate a particular brain region. Additionally, these studies may explain why putative neurodevelopmental insults initially result in only subtle pre-morbid clinical signs until schizophrenia becomes fully manifest in early adolescence.

Conceptual Models of Schizophrenia

The integration of data from multiple dimensions into conceptual models of the etiology and/or pathophysiology of schizophrenia provides a framework for organizing research approaches and understanding the significance of new findings as they enter the literature. Dr. Robin Murray presented a neurodevelopmental model that strives to integrate information on putative risk factors and the genetic predisposition that is observed in patients with schizophrenia. He argued that schizophrenia is the end result of early central nervous system (CNS) insults (e.g., obstetrical complications) superimposed on a genetic vulnerability, which then lead to disturbed social and scholastic functioning in childhood and adolescence. The combination of these factors leads to an increased likelihood of further insults (e.g., substance abuse) and decreased protective factors (e.g., an enriched social environment). The combination of these events is hypothesized to result in the expression of schizophrenia. The model argues that people at risk are not "doomed from the
womb,” but rather that schizophrenia is the manifestation of the accumulation of multiple risk factors. If the latter, more optimistic perspective is correct, then early detection and prevention programs could be developed to minimize the exposure of the “at-risk” individual to additional risk factors and CNS insults.

Dr. Lieberman reviewed the hypothesis that a significant proportion of patients may have a progressive form of the illness. He noted that there is evidence of clinical deterioration over the first 5 to 10 years of illness, with decreased social adjustment, level of functioning, and treatment responsiveness, and a progressive development of more severe subtypes (e.g., hebephrenia, catatonia, and a deficit form of schizophrenia). There are also concurrent changes in a number of biological measures. Eye movement abnormalities may be more common in chronic than in first-episode samples, and the amplitude of the event-related brain potential—P300—may deteriorate over time. The results from longitudinal structural imaging studies are relatively inconsistent, but when progressive changes are observed, they are usually associated with clinical deterioration or increased number or duration of psychotic episodes. Dr. Lieberman noted that, in his first-episode studies, nonremitting patients tended to have an increase in ventricular and a decrease in cortical volumes over time. The latter observation has been replicated in an independent first-episode sample from Stony Brook (Dr. Lynn DeLisi) and in a 2-year followup of patients with adolescent-onset schizophrenia (Dr. Judith Rapoport). These progressive effects, also noted in patients with more chronic forms of schizophrenia (Dr. David Mathalon), suggest a modest but diffuse decline in brain volume and a ventricular enlargement in schizophrenia that are in excess of those associated with normal aging. The mechanisms underlying these putative progressive changes are unknown. Dr. Lieberman proposed synapsin 1 as a potential candidate that warranted further investigation. Alternatively, this effect may reflect a neurodegenerative process that is superimposed on a primary, neurodevelopmental lesion. Down’s syndrome (DS), which is associated with the age at onset of Alzheimer’s disease in the early forties, is a good disease model for evaluating the relative contributions of neurodevelopment and neurodegeneration. In a comparative magnetic resonance imaging (MRI) study of patients with schizophrenia and patients with DS, Dr. Godfrey Pearson found that DS patients had a more diffuse pattern and more pronounced cerebral abnormalities than the schizophrenia group.

Drs. Francine Benes and David Lewis have elucidated several aspects of the microcircuitry of cortical layer II (Dr. Benes) and III (Dr. Lewis) of the prefrontal cortex. These microcircuits undergo considerable changes during the various stages of normal cortical development. Subtle abnormalities have been noted in the structure and axon-dendritic connections of these circuits: These abnormalities could provide a neuroanatomical basis for the observed alterations in information processing in patients with schizophrenia. Further knowledge of the normal circuitry can be used to evaluate the impact of putative etiological agents on the structure of these circuits. For example, perinatal insults (e.g., obstetrical complications) are commonly associated with increased levels of cortisol. Cortisol administered prenatally increases the number of dopaminergic connections in nonpyramidal cells, which parallels the increased number of tyrosine hydroxylase varicosities observed in prefrontal cortex nonpyramidal cells in patients with schizophrenia.

Etiology

The ability to scan the human genome and the ongoing Human Genome Project have brought the dream of discovering the genes involved in the etiology of schizophrenia significantly closer to realization. There have been two major approaches for investigating the genetics of schizophrenia. The first is linkage analysis. There are now over 3,000 genetic markers for the human genome. These markers have a known location and can be used to scan the genome at relatively small intervals. A number of ongoing projects in the United States and Europe are using these markers to scan the entire genome for linkages with schizophrenia. To date, chromosomes 5, 6, 8, 13, and 22 have had replicated linkages. The existence of multiple replicated linkages strongly supports the supposition that schizophrenia is at least a genetically heterogeneous disorder. The existence of etiological and pathophysiological heterogeneity remains to be determined.

The presence of a linkage leaves the field with the still daunting task of trying to identify which of the approximately 400 possible genes is responsible for causing schizophrenia. The eventual mapping of the entire genome will greatly facilitate this endeavor. In the meantime, association studies can attempt to more narrowly define the chromosome region containing the gene of interest. A significant association with a candidate gene or marker locus will be observed only if the gene or marker is (or is physically close to) the actual gene. The use of this strategy was described by Drs. Vishwajit Nimgaonkar, Padraig Wright, and Wolfgang Maier. Drs. Nimgaonkar and Wright both reported negative associations with human leukocyte antigen (HLA) markers. These negative associations suggest that the presence of genes in this region of chromosome 6 reduce the susceptibility of developing schizophrenia. Dr. Maier also reported the presence of significant associations with
chromosome 6 markers. The associations were compatible with an association with a gene in the HLA region, but in contrast to the above studies, were in the positive direction.

Association studies may also provide insight into the connection between potential candidate genes and clinical characteristics of schizophrenia. Approximately 20 to 30 percent of patients with schizophrenia are characterized by the presence of primary, enduring negative or deficit symptoms. These symptoms have been hypothesized to be related to disturbances in either DA or serotonin (5-HT) neurotransmitter systems. However, Dr. Robert W. Buchanan reported a lack of association with polymorphisms of the 5-HT₂A, 5-HT₂C, D₃, and D₄ receptors. There has also been a series of studies examining the relationship of receptor polymorphisms and response to clozapine. Dr. Maria Arranz reported an association between clozapine response and polymorphisms in the promoter region and 5-HT₂A receptor gene. However, Dr. David Pickar failed to observe an association between clozapine response and polymorphisms of the 5-HT₂A, 5-HT₂C, D₃, and D₄ receptors. The conflicting results may be, in part, attributable to differences in the definition of clozapine response, with Dr. Pickar basing response on the results derived from double-blind clinical trials.

A major problem in linkage and other genetic studies is how to define the phenotype. Family studies suggest that, at a diagnostic level, the phenotype extends beyond schizophrenia and includes schizoaffective and schizophréniform disorders, other nonaffective psychotic disorders, and schizophrenia spectrum personality disorders. Symptom complex, neuropsychological, psychophysiological, and electrophysiological measures may also define a phenotype. Eye-tracking abnormalities and negative symptoms are two examples of this approach. Dr. Sherry Leonard presented recent results on the use of abnormal inhibition of P50, an early auditory evoked potential response to define the phenotype. P50 abnormality is observed in a large proportion of patients with schizophrenia. The P50 response is regulated by cholinergic mechanisms, acting at the α-7 nicotinic receptor. In a linkage study, Dr. Leonard reported that polymorphisms of chromosome 15 markers, in close proximity to the α-7 nicotinic receptor, were linked with P50 abnormalities in families with multiple cases of schizophrenia. If replicated, this could lead to the direct identification of a gene etiologically related to schizophrenia.

An alternative hypothesis for the observed familial transmission of schizophrenia is anticipation secondary to the presence of expanded trinucleotide repeats. Dr. John B. Vincent presented the results from an extensive set of experiments designed to detect the presence of expanded CAG/CTG trinucleotide repeats in schizophrenia. The results were uniformly negative, providing strong evidence against the involvement of this repeat in schizophrenia.

**Pathophysiology**

**Neuroanatomy.**

**Structural imaging studies.** Structural imaging techniques, especially MRI, provide a methodology for comprehensive morphological assessments of cortical and subcortical structures in large groups of patients and carefully selected comparison subjects. Moreover, the capability to conduct concurrent and prospective clinical evaluations enhances the ability to examine structure and behavior relationships. Structural imaging studies can guide subsequent postmortem investigations and elucidate the ultrastructural changes underlying the observed structural alterations.

Several groups have developed techniques to enable whole brain comparisons of patients with schizophrenia and normal comparison subjects. Dr. Peter Falkai described a novel technique comparing individual three-dimensional surface brain reconstructions with the group mean brain surface reconstruction. Normal variations in surface contour, which differed across genders, were greatest in higher cortical association areas. First-episode patients with schizophrenia exhibited decreased variability in these regions when compared with normal controls. Dr. Robert B. Zipursky also found gray matter changes in first-episode patients, with global decrements in gray matter volume and increased ventricular volume. Dr. Tommoy Sharma examined alterations in regional gray matter on brains transformed on a pixel-by-pixel basis into a standardized stereotactic space. There was a significant reduction in global gray matter density, with significant regional intensity differences observed in bilateral temporal pole and insula and in the left prefrontal cortex.

Several groups reported studies designed to examine the presence of focal changes. Dr. Patrick Barta replicated an earlier study observing reversal of planum temporale (PT) surface area asymmetry in patients with schizophrenia. In contrast to the surface area measures, patients with schizophrenia had bilateral reductions in PT volume, with abnormal thinning of the right PT. Dr. John Csernansky used three-dimensional surface reconstructions of the hippocampus to demonstrate that the 8 percent volume difference observed between patients and normal controls was not attributable to local distortion within any specific subregion of this structure. Dr. Katalin Vladar reported on a reliable procedure to parcel-
late the prefrontal cortex into four subregions and used this technique to document a significant bilateral reduction in inferior prefrontal (i.e., Broca's area) gray matter, in the absence of significant differences in prefrontal total gray matter volume. Dr. Tyrone D. Cannon reported that patients were more likely to have larger cerebrospinal fluid volumes than their unaffected siblings, with the primary difference between the groups in the left hemisphere, particularly in the frontal lobe.

Relatively few studies have examined the relationship between the morphological abnormalities observed in patients with schizophrenia and the severity of illness. Dr. Laura Marsh reported that volume alterations in cortical gray matter are relatively independent of illness severity, with both severely ill, chronic State hospital patients and moderately ill Department of Veterans Affairs (VA) patients exhibiting smaller temporal lobe and frontal-parietal gray matter volumes. Dr. Robert M. Bilder examined cortical, mesiotemporal, caudate nucleus, and ventricular volumes in patients with schizophrenia, schizophreniform, and schizoaffective disorder, and psychotic and nonpsychotic affective disorders and in normal controls. The more chronic patient groups were more likely to exhibit ventricular enlargement. However, there were no differences in cortical volume across the groups, including the patients with chronic schizophrenia. The latter finding is in contrast to the other reports of cortical volume changes in patients with schizophrenia. Dr. Joseph Ventura, using the Proxy for the Deficit Syndrome to identify patients with prominent negative symptoms (and who may have a more severe course), reported that negative symptoms were associated with lower frontal total and white matter volumes.

Postmortem studies. The results of the above-mentioned studies provide strong support for cortical changes in patients with schizophrenia, particularly in the higher association cortices. These observations are further supported by the results of postmortem studies. Dr. Peter Falkai reported that male patients with schizophrenia have smaller prefrontal lobes than male control subjects and that patients with schizophrenia have decreased cell packing density in Brodmann Area (BA) 10. The sample was too small to determine if there were any gender effects in cell density. Dr. Natalya A. Uranova examined the postsynaptic density of axospinous and axodendritic synapses in BA 10. Patients with schizophrenia had significantly increased postsynaptic densities and larger postsynaptic spines, with the changes most marked in patients with predominant positive symptoms. By contrast, patients with predominant negative symptoms had fewer and smaller mitochondria in the presynaptic axon terminals and smaller postsynaptic spines. The differential pattern of changes associated with positive and negative symptoms is consistent with different pathophysiological mechanisms underlying their expression.

In light of recent hypotheses proposing a central role of glutamate in the etiology of schizophrenia, James H. Meador-Woodruff examined the density and messenger ribonucleic acid (mRNA) expression of glutamate receptors. There were significant differences in the expression of the NMDAR1 and NMDA2A receptor subunit mRNA in the prefrontal cortex. There were no significant differences in prefrontal cortex o-amino-3-hydroxy-5-methyl-4-isoxazole-4-propionic acid (AMPA) binding or mRNA expression.

However, Dr. Joseph N. Pieri failed to find any significant difference in mean somal size of prefrontal layer III pyramidal cells. Using immunofluorescence, Dr. Maree J. Webster examined the signal intensity of THY-1 and L1 (neural adhesion molecules) in the prefrontal cortex. There were no significant differences in the distribution of these molecules in the brains of patients with schizophrenia and normal controls. Similarly, Dr. Paul Harrison and colleagues failed to find any differences in markers of synaptogenesis and plasticity in the prefrontal cortex (BA 46).

In summary, these results support the involvement of higher association cerebral cortex in schizophrenia. Postmortem studies are inconsistent in addressing whether this involvement reflects abnormal plasticity or altered connectivity. The majority of the studies presented restricted their examination to the prefrontal cortex and did not examine whether the prefrontal cortex is uniquely involved or whether similar microscopic changes occur in the temporal and parietal higher association areas. There is also the question of whether observed changes are primary or are in response to primary changes elsewhere in the brain.

Neurochemistry.

Animal models. Although the DA hypothesis remains the most influential neurochemical pathophysiological hypothesis of schizophrenia, the focus of the field has expanded beyond DA to include, among others, the study of gamma-aminobutyric acid (GABA)ergic, glutamatergic, noradrenergic, and serotonergic neurotransmitter systems. This expansion of focus has been stimulated in part by an increased understanding of the complex interactions among the different neurotransmitter systems. The study of the normal neurochemistry of the brain provides a necessary framework for the interpretation of neurochemical studies of patients with schizophrenia. Two presentations investigated the interrelationships among structures hypothesized to be involved in the pathophysiology of schizophrenia. The first study examined the regulation of nucleus accumbens (NAcc) activity (Dr. Holly
Moore). The NAcc receives afferent projections from the amygdala, prefrontal cortex, and midbrain DA cells. Stimulation of the amygdala results in an increased likelihood that prefrontal stimulation of the NAcc will elicit spikes in the NAcc. This interaction is modified by DA agonists and a maldevelopment of the hippocampus and other limbic areas. Dr. Bhasskar S. Kolachana examined the interaction between the prefrontal cortex, hippocampus, and caudate. In adult monkeys with neonatal lesions of the medial temporal-limbic region, which includes the hippocampus, injection of amphetamine caused increased DA release in the caudate. By contrast, surgical removal of the same region in adult monkeys results in normal down-regulation of caudate DA. Both of these studies point to the fact that abnormal development of the limbic system can lead to disruption of cortical regulation of subcortical structures.

Dr. Bryan K. Yamamoto has examined the interaction of norepinephrine (NE) and DA in the prefrontal cortex. NE reuptake inhibitors lead to increased extracellular DA, and noradrenergic-specific neurotoxins abolish the effects of these reuptake inhibitors. These results suggest that the NE reuptake mechanism plays an important role in regulating extracellular DA concentrations, with the level of extracellular DA related to the activity of the noradrenergic system. Dr. Walid M. Abi-Saab reported on the serotonergic modulation of prefrontal cortex GABA activity. Serotonergic 5-HT$_{2a}$ and 5-HT$_{2c}$ agonists stimulate nonpyramidal cell GABA activity. This increased activity is blocked by serotonergic 5-HT$_{2a}$, but not 5-HT$_{2c}$, antagonists.

**Postmortem studies.** Neurochemical studies also help delineate the significance of structural imaging and postmortem studies. Dr. Joel Kleinman presented an overview of postmortem neurochemical studies of patients with schizophrenia. In a series of studies, reductions of cholecystokinin, glutamate transporter, growth-associated phosphoprotein (GAP)-43, brain derived neurotrophic factor (BDNF), and limbic associated membrane protein (LAMP) mRNA have been observed in either hippocampal or cortical structures. Dr. David A. Lewis presented preliminary data on dopaminergic fiber number in the prefrontal cortex. Patients with schizophrenia have decreased dopaminergic fibers in layers III and VI of the prefrontal cortex. These decrements were evident in a subgroup of pyramidal cells. Selective reductions in the axon cartridges of chandelier neurons (specialized GABA containing cells that are inhibitory to pyramidal neurons) were also observed.

**Nuclear magnetic resonance spectroscopy.** Magnetic resonance spectroscopy (MRS) allows for the in vivo assessment of brain chemistry. Dr. Constance M. Moore examined the relative concentrations of choline-containing compounds in patients with schizophrenia and in normal controls. Left temporal lobe choline/creatine ratios were decreased in patients; the difference was not attributable to differential tissue loss between the two groups. In a complementary study by Dr. Kelvin Lim, loss of cortical gray matter in male schizophrenia patients was not associated with reduction in N-acetyl aspartate (NAA), suggesting that the observed volumetric alteration was attributable to some process affecting both neuronal and glial elements equally rather than to a neurodegenerative process in which neuronal loss is replaced by glial proliferation. In a preliminary study by Dr. Peter Buckley, frontal lobe decrements in NAA/choline ratios were observed in adolescents with schizophrenia to an extent comparable to those of adolescents with autism (an unequivocal neurodevelopmental disorder). In another MRS study for adolescent-onset schizophrenia, Dr. Sophie Frangou observed a different pattern of age-related decreases in choline-creatinine ratio in patients with schizophrenia than in normal controls. Dr. Ramesh Eluri examined the NAA, choline, and myoinositol (MI) concentrations in the pons and cerebellum. MI/creatinine ratios were increased in the right and left cerebellum and pons, whereas choline/creatine ratios were increased in the right cerebellum and pons. The data provide increasing evidence for the possible role of the cerebellum in schizophrenia.

In summary, these studies increase our understanding of normal brain chemistry and begin to delineate neurochemical changes, which may be related to the altered brain morphology documented in structural studies. In addition, they provide an empirical framework for understanding functional imaging studies using pharmacological probes and for rational drug development.

**Neuropsychology/Cognitive Psychology**

Patients with schizophrenia are characterized by a broad range of cognitive abnormalities. In contrast to positive symptoms, these impairments are relatively unaffected by available treatments for schizophrenia. Although the differential treatment responsiveness of positive symptoms and cognitive impairments suggests that different mechanisms may underlie their production, the relationship between these two manifestations of schizophrenia has not been clearly elaborated, nor have the cognitive underpinnings of other symptom complexes been delineated. There is also little information on whether cognitive impairments in schizophrenia reflect a generalized dysfunction of the brain, or whether the observed global dysfunction is the manifestation of altered function of a smaller number of basic cognitive processes (e.g., work-
ing memory). Finally, the neuroanatomy of cognitive impairments occurring in schizophrenia remains to be elucidated. These questions were a major focus of this year's Congress meeting.

In a thought-provoking plenary lecture that was aptly titled "If Brain Scanning Is the Answer, What Is the Question?" Dr. Kosslyn emphasized the importance of meticulous study design when conducting research on cognitive neuroscience. Focusing on the complexity of the visual system, he stressed that our research should be driven by fundamental questions that can be appropriately addressed. He suggested that such critical questions might include how mental events are implemented in the brain, which brain regions implement the systems necessary to carry out complete cognitive tasks, and how this circuitry may be altered under different circumstances.

Dr. Holzman provided a historical overview of the converging paths of cognition, neuroscience, and schizophrenia. He also emphasized how progress in the study of cognitive abnormalities in schizophrenia requires a thorough understanding of normal brain function. A major construct that has guided recent investigations is working memory.

Dr. Michael Green provided an authoritative review of the literature concerning the relative impact of cognitive, positive, and negative symptoms on measures of social problem solving, social skills acquisition, and global psychosocial functioning. Memory impairments were most closely related to abnormalities in all three aspects of functioning, while negative symptoms were associated with impaired problem solving and skills acquisition. The relationships for positive symptoms were more tenuous. Dr. Green postulated a strong relationship between neurocognition, negative symptoms, and functional outcome in schizophrenia. He made a plea for a stronger emphasis on the role of cognitive impairment in the nosology of schizophrenia.

Working Memory. Dr. Patricia Goldman-Rakic provided an update on the modulatory role of DA, acting at the D₁ receptor, on working memory function in the prefrontal cortex. Specific prefrontal regions are associated with different forms of working memory (e.g., spatial versus visual). There is also specialization within each prefrontal region; prefrontal pyramidal cells and interneurons form microcircuits with functional specificity. These microcircuits are regulated by DA through the D₁ receptor.

Patients with schizophrenia have been shown to exhibit auditory, spatial, and verbal working memory impairments. Dr. Stephan F. Taylor suggested that patients with schizophrenia are relatively more impaired on verbal than spatial working memory tests. Judy Rubinsztein argued that current definitions of working memory are too broad and inclusive. If working memory is defined more narrowly and according to Alan Baddeley's original formulation of the concept (Baddeley 1983), then patients with schizophrenia do not exhibit working memory impairments. The results of the latter study raise a concern about the nature of the cognitive processes being subsumed under the rubric of working memory and reinforce the need to clearly define the construct under investigation.

Cognitive Models of Symptom Complexes. Over 20 factor-analytic studies have examined the pattern of co-segregation of the symptoms of schizophrenia. The majority of these studies have found that the symptoms form three semi-independent factors: (1) hallucinations and delusions; (2) disorganized behavior, including positive formal thought disorder (FTD), bizarre behavior, and inappropriate affect; and (3) negative symptoms. The increased understanding of normal cognitive functioning has led to increased sophistication of cognitive models of symptom complexes. Dr. Manfred Spitzer presented a model for a component of the disorganized behavior symptom complex, FTD. The model is based on the observation that patients with FTD have increased, rather than decreased, semantic priming during lexical decision making. The associations among words can be represented as a probabilistic network, given the relative likelihood of which words and how many words are associated with a stimulus work. In normals, discrete aspects of this semantic network are activated, whereas patients with FTD have a more widespread activation of the network. The overactivation of the semantic network, perhaps combined with impairments in working memory, is hypothesized to result in the various clinical manifestations of FTD. Further, Dr. Spitzer postulated that these neural networks were modulated by DA function. He presented data showing that indirect priming in normal subjects was attenuated during an infusion of t-dopa.

Dr. Terry Goldberg observed that patients with schizophrenia perform more poorly on semantic than on phonological fluency tasks. There is also a differential activation of the middle and inferior temporal gyri during the performance of semantic and phonological fluency tasks, with increased activation of these regions during semantic tasks. Patients with schizophrenia with FTD exhibit negative priming on medium- and high-association tasks. These observations suggest that FTD is related to functional alterations of the middle and inferior temporal gyri, which lead to impairments in the semantic processing system. Dr. Gina R. Kuperberg found that patients with FTD were less affected by pragmatic, semantic, or syntactic context anomalies than patients without FTD and normal controls. They were also more likely to produce more out-
of-category errors on semantic fluency tests. These results are consistent with those of Dr. Goldberg and support the hypothesis that patients with FTD have difficulty in using linguistic context to process and produce speech.

Dr. Jonathan D. Cohen has articulated a theoretical model that emphasizes the central role of processing context during task performance. The prefrontal cortex is hypothesized to play a major role in this process. If prefrontal cortex function is impaired in patients with schizophrenia, they would be expected to perform more poorly on tasks that require context to be maintained over a delay period. The results of studies that examined performance on tasks modified to emphasize the importance of maintaining context are consistent with this hypothesis. However, Dr. Martin Harrow examined the relationship between FTD and maintaining context and found that FTD was not related to impairments in holding contextual material in working memory.

Dr. David Copolov compared hallucinating and non-hallucinating patients with normal controls. Hallucinating patients were more likely than either of the other groups to exhibit poorer performance on tasks of central auditory processing. The pattern of results suggested that hallucinations are associated with nonspecific disturbances in central auditory processing, predominantly affecting the right hemisphere or interhemispheric transfer pathways. Dr. Emmanuelle Peters reported that delusions were associated with increased negative priming (i.e., increased response latency to a previously ignored stimulus). Dr. Richard S.E. Keefe observed that patients with hallucinations and delusions of insertion or control were less likely to be able to distinguish between internally and externally generated stimuli.

Dr. Sohee Park found that baseline negative, but not positive, symptoms predicted working memory at followup. However, the significance of this relationship is unclear, since primary negative symptoms were not discriminated from secondary negative symptoms.

In a study that examined the relationship of performance on a task assessing visual perception and memory and the three major symptom complexes, Dr. Ryosuke Izawa found that behavioral disorganization, including FTD but not the other two complexes, was related to poor test performance.

In summary, there is converging evidence suggesting a relationship among FTD, inferior temporal lobe structures, and impairments in semantic processing (see below). The cognitive underpinnings of other symptoms or symptom complexes is less clear.

**Neuroanatomy of Cognitive Impairments.** Positron emission tomography (PET) and functional MRI are used to examine the functional neuroanatomy of cognitive impairments in patients with schizophrenia. Dr. Peter F. Liddle identified a cardinal site in the left lateral frontal cortex that was activated in all subjects during semantic fluency task performance and examined the relationship among different brain regions and this cardinal site in patients with schizophrenia and normal controls. Patients with schizophrenia had increased frontal-temporal and decreased frontal-thalamus and frontal-precuneus blood flow correlations. Dr. Liddle proposed that these findings were further evidence of a functional dysconnectivity in schizophrenia. Dr. Cameron S. Carter found that, during performance of a modified version of the Stroop test (Stroop 1935), patients fail to activate the anterior cingulate cortex and to suppress the fusiform cortex to the same extent as normal controls. However, both groups show a similar inverse relationship between blood flow in the two regions and Stroop errors. Dr. Brendan T. O’Sullivan examined blood flow during the performance of a series of visual attention and working memory tests. He found that patients exhibited a different pattern of activation during divided and switching attention tests. Patients activate bilaterally the middle frontal region, whereas normal controls activate only the right middle frontal region. Further, normal controls activate the left inferior frontal region, right anterior cingulate, and bilateral thalamus; these regions are not activated in patients with schizophrenia. Dr. Deborah A. Yurgelun-Todd examined blood flow with functional MRI during supraspan memory performance and found that male patients had greater temporal lobe activation than normal controls during test performance, despite impaired performance. The effect was not observed in female patients.

**Natural History of Cognitive Impairments.** Finally, a series of presentations described the developmental course of cognitive impairments in patients with schizophrenia. Dr. Robert F. Asarnow presented a follow-back study that documented developmental delays in children who went on to develop schizophrenia. The presence of these delays was associated with later difficulties in learning new skills. In a prospective cohort study of almost 10,000 subjects, Dr. Cannon reported that both preschizophrenia children and their unaffected siblings exhibited cognitive impairments, with greater impairment in the preschizophrenia children being associated with a history of perinatal hypoxia. Dr. Jill M. Goldstein is conducting a longitudinal study, as part of the National Collaborative Perinatal Project, of the offspring of parents with schizophrenia. These children will be followed until age 37, providing an opportunity to assess the interaction between genetic predisposition and perinatal complications and the development of cognitive impairments in children who are at high risk for having schizophrenia. The children...
have been prospectively followed through age 7, with preliminary analyses revealing that IQ differences do not become apparent until this age.

The observations of premorbid cognitive impairments are consistent with first-episode studies that have documented cognitive impairments at the time of onset of positive symptoms. Dr. Sam B. Hutton demonstrated that first-episode patients exhibit impairments on tasks that require a planned or ordered response for efficient performance. Dr. Gretchen Haas reported that patients in a Pittsburgh study on the first episode of schizophrenia showed early improvement in attention and concentration functions with treatment, while any improvement in other cognitive functions, such as memory, was more gradual. One study addressed the question of whether patients with schizophrenia exhibit a progressive decline in cognitive abilities. In a followup study of the Stony Brook First-Episode Study, Dr. Anne L. Hoff failed to observe any significant differences in cognitive decline between patients and normal controls. Dr. Murray suggested that once cognitive impairment is established (even premorbidly), it does not appear to progress over the course of the illness and is more suggestive of a static encephalopathy. Further results from ongoing epidemiological and first-episode studies will help clarify this important issue.

Electrophysiology

Patients with schizophrenia are characterized by impairments in attention and information processing, eye movements, and sensory gating. Abnormalities in the processing of information may be reflected in event-related potentials or other evoked potentials. Several of these abnormalities have been argued to represent liability and/or phenotypic markers. Their study represents an alternative approach for investigating the cognitive abnormalities observed in patients with schizophrenia.

There are a number of reports of P300 abnormalities in schizophrenia, including abnormal amplitude in the left temporal lobe. Dr. Dean F. Salisbury reported that left temporal lobe P300 abnormalities are present in first-episode patients. Dr. Daniel Umbricht compared the P300 amplitude in patients with schizophrenia and normal controls during the performance of the AX version of the Continuous Performance Test (Rosvold et al. 1956). Normal controls have increased P300 amplitude for validly cued nontargets. This effect is not observed in patients. These results suggest that patients are less responsive to discrepancies between expected and actual stimuli. Patients with schizophrenia also exhibit impairments in automatic sensory gating, as manifested by a lack of decrement in P300 to an auditory startling stimulus preceded by an auditory warning stimulus (Dr. Judith M. Ford).

P50 abnormalities have been argued to be a phenotypic marker of schizophrenia, and linkage with chromosome 15 has been reported (see above). Dr. Brett Clementz conducted a study examining P50 in patients, their family members, and normal controls. Patients and family members both showed abnormal P50 suppression, which provides further support for the use of P50 as a phenotypic marker of schizophrenia. The severity of the P50 abnormality may vary with gender, with female patients having more normal values (Dr. Sophia Vinogradov).

One of the most studied psychophysiological measures in schizophrenia is smooth pursuit eye tracking. A significant proportion of patients with schizophrenia exhibit altered smooth pursuit, with these abnormalities present in first-episode (Dr. Hutton) and chronic patients. Dr. Diane C. Gooding examined the relationship between eye-tracking abnormalities and neuropsychological function. In patients who were receiving conventional antipsychotics, there was an association between eye-tracking abnormalities and impaired performance on putative measures of prefrontal cortex function. By contrast, in patients who were being treated with the atypical antipsychotic clozapine, there was an association between eye-tracking abnormalities and impaired performance on putative measures of temporal lobe function. These results suggest that eye-tracking abnormalities may vary with treatment responsiveness.

Psychopathology

Negative Symptoms. The three-symptom complex model is an influential organizing framework for the study of psychopathology in patients with schizophrenia. This finding has already been demonstrated in the cognitive studies of the symptoms of schizophrenia (see above). Dr. William T. Carpenter, Jr. put forth the proposition that the presence of the negative symptom complex, when restricted to include only primary, enduring negative or deficit symptoms, defines a specific disease entity within the clinical syndrome of schizophrenia. Dr. Paul J. Scully presented 12-year followup data suggesting that the duration of untreated psychosis (undefined) predicted the presence of negative, but not positive, symptoms and cognitive impairment at followup. The effect of baseline negative symptoms on this relationship was not presented. Dr. Donald M. Quintan presented the correlations among negative symptoms at baseline and at 24-month followup. The highest correlation was seen for avolition; this construct also showed the highest correlation with neuropsychological test performance. The data suggest that measures of avolition may have the highest temporal stability. Dr. Jane Edwards presented three methods for attempting...
to identify patients with persistent or enduring negative symptoms. The prevalence rate ranged from 5.3 to 21 percent, depending on the method. Regardless of method, patients with persistent negative symptoms had poorer premorbid adjustment, quality of life, and global functioning.

The field continues to struggle with the distinction between primary and secondary negative symptoms. Despite the extensive data from multiple centers on this issue, there was no attempt to differentiate primary from secondary negative symptoms in the majority of the presentations. The failure to do so continues to complicate our understanding of a core component of schizophrenia psychopathology.

Neuroanatomy of Symptom Complexes. In a series of functional imaging presentations, attempts were made to elucidate the neuroanatomy of symptom complexes. Dr. Michael Flaum examined the relationship between the three-symptom complexes and blood flow and found a significant inverse relationship between blood flow in Heschl’s gyrus and hallucinations. Disorganized behavior was inversely correlated with anterior cingulate blood flow, whereas negative symptoms were related to decreased blood flow in the frontal region, as well as the cerebellum and pons. Dr. Copolov exposed four nonhallucinating patients to external auditory stimulation: The exposure failed to produce blood flow changes in the superior temporal gyrus similar to those observed in three patients with auditory hallucinations. Dr. Philip McGuire examined blood flow in six patients who were responding to the Thematic Apperception Test (Murray 1943). Thought-disordered responses were associated with increased blood flow in the fusiform gyrus. In normal controls, this area is activated when subjects are confronted with anomalous sentences. FTD was also inversely associated with blood flow in the inferior frontal and posterior cingulate gyri (regions normally associated with appropriate word selection) and in the superior temporal gyrus (a region normally associated with the monitoring of speech). These observations are consistent with results from cognitive studies of FTD and further implicate abnormalities in semantic processing and temporal lobe structures in the production of FTD.

Neurological Signs. Patients with schizophrenia are more neurologically impaired than other psychiatric patients and normal controls. Family studies and the study of unaffected relatives suggest that neurological signs may also be a phenotypic marker of schizophrenia. Neurological signs are present in first-episode patients, and their presence is associated with poorer neuropsychological test performance but not with medication side effects (Dr. Friedreich J. Mohr). Dr. Robert C. Smith conducted a 3-year study of the stability of neurological signs and reported that their presence is unaffected by changes in psychopathology or treatment with atypical antipsychotics. The presence of neurological signs was related to poorer response to risperidone and inversely correlated with cigarette smoking. These two studies provide further support for the theory that neurological signs represent a trait characteristic that is minimally affected by antipsychotic treatment.

Symptoms as Phenotypic Markers. There is clear evidence that the phenotypic expressions of schizophrenia genes extend beyond the diagnosis of schizophrenia to include other nonaffective psychotic and schizophrenia spectrum personality disorders. A series of studies addressed the question of whether specific symptoms may define a phenotype. In an examination of the biological and adoptive relatives of adoptees with either schizophrenia or normal controls, Dr. Loring Ingraham reported an increased occurrence of autistic thinking, suspiciousness, and introverted/asocial behavior in the biological relatives of patients with schizophrenia. However, the type of symptoms in relatives did not correlate with the type of symptoms in patients. In two related studies, Dr. Deborah L. Levy also found that interpersonal behavior differentiated the relatives of patients with schizophrenia from normal controls. Dr. Kenneth Subotnik observed that relatives of patients with schizophrenia scored abnormally high on the Minnesota Multiphasic Personality Inventory Suspiciousness scale; the relatives also scored higher on the schizophrenia and hostility scales. In a study of first-episode patients, there were no differences at discharge in the symptomatic presentation of patients with a positive versus negative family history (Dr. Agneta Nilsson).

A complementary approach to investigating the genetic influence on symptom expression is to study schizotypal patients. Dr. Meinte G. Vollena reported that, consistent with the results of factor-analytic studies in schizophrenia, a three-factor structure optimally describes the occurrence of schizotypal symptoms. The occurrence of schizotypal symptoms in the family members of patients with schizophrenia may vary with gender, with female relatives no more likely to have schizotypal symptoms than female normal controls (Dr. William S. Kremen). There is apparently no difference in neurological abnormalities (Dr. Thordur Sigmundsson) or dissociative learning (Dr. Ana M. Serra) in family members who meet versus those who do not meet criteria for schizotypal personality disorder. In a study of a community sample of patients with schizotypal symptoms, Helene Adami reported that relatives had increased positive and decreased negative symptoms as compared with the relatives of familial schizotypal patients. In an MRI study,
Dr. Chandlee Dickey noted a reduction in gray matter volume of the left superior temporal gyrus of patients with schizotypal personality disorder; these volume changes were correlated with severity of thought disturbance.

In an interesting study, in accordance with neurodevelopmental hypotheses of schizophrenia (see above), Dr. Peg Nopoulos observed that male patients with schizophrenia are statistically shorter, although this effect was evenly distributed and represented a (schizophrenia) group shift to the left rather than a subgroup effect. However, those patients in the lowest quartile exhibited delay in developmental milestones and poorer premorbid social and scholastic performance. These results suggest that a subgroup of patients may manifest a global impairment in growth and function.

**Treatment**

**Psychopharmacology.** Pharmacological agents remain the primary treatment modality for schizophrenia. An increased understanding of brain neurochemistry holds the promise that more specific agents will become available; agents that are effective not only for positive symptoms, but for negative symptoms and cognitive impairments. In the meantime, a number of new agents, based on the pharmacological profile of clozapine, have been or are about to be approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia. These agents are at least as effective as conventional antipsychotics for positive symptoms, but offer a more benign side-effect profile, including decreased EPS.

**Preclinical pharmacology.** The study of normal brain chemistry (see Pathophysiology: Neurochemistry section) and the influence of antipsychotic medications on normal brain chemical processes is essential for understanding the primary and secondary effects of the schizophrenic disease process on brain function and the direct and indirect effects of drugs on brain chemistry in patients with schizophrenia. Dr. Elizabeth Abercombie discussed the role of D1 and D2 receptors in the basal ganglia regulation of the flow of information to the thalamus. The caudate and putamen are part of a series of parallel neural circuits that interconnect the cerebral cortex and the thalamus. These neural circuits subserve a broad range of cognitive and motor behaviors. There are two efferent pathways from the caudate/putamen to the thalamus: the direct pathway, which is modulated by D1 receptors, and the indirect pathway, which is modulated by D2 receptors. In addition to DA, these pathways are also under the influence of GABA, glutamate, and acetylcholine. The direct and indirect pathways may serve as the substrate for the therapeutic and adverse effects of antipsychotic medica-

This observation suggests a role for these regions in the regulation of the flow of information to the thalamus. The role of the D1 receptors in the basal ganglia may mediate the antipsychotic effects of these agents. D1 receptors also play a major role in regulating dopaminergic activity in the cortex, whereas both D1 and D2 receptors regulate striatal DA activity (Dr. Elizabeth Pechek). Dr. H. Christian Fieig observed the importance of molecular biology techniques for examining the mechanism of action of antipsychotics. Antipsychotics produce neuroanatomically localized expressions of immediate early genes (e.g., c-fos). Both conventional (i.e., haloperidol) and atypical antipsychotics (i.e., clozapine) produce increased c-fos expression in the NAcc and lateral septal nucleus. The NAcc receives substantial dopaminergic input; the lateral septal nucleus has been implicated, through depth electrode recordings, as being important in producing positive symptoms. However, c-fos and D3 mRNA labeling of cells in these two regions suggests that clozapine targets different neuron populations than haloperidol. In addition, clozapine, but not haloperidol, produces increased c-fos expression in the medial prefrontal cortex. These differences in metabolic activity may be related to clozapine's superior positive symptom efficacy.

How antipsychotics exert their therapeutic effect is unknown. A leading hypothesis is depolarization blockade of DA neurons. Dr. Anthony Grace presented an update of the hypothesis, including new data addressing potential concerns regarding the artifactual nature of the phenomenon. Alternatively, the mechanism of action of antipsychotics may be related to their effect on other neurotransmitter systems. Dr. Rex Y. Wang presented data documenting the effect of antipsychotic medications on NMDA-induced inward current, through their action at the 5-HT{sub}2a receptor. Dr. Cheryl Young examined the possibility that neurotensin, which is co-localized with DA in the mesocortical DA system, may mediate the antipsychotic effect of atypical antipsychotics. Neurotensin agonists produce a similar pattern of c-fos activation as clozapine in the prefrontal cortex and NAcc. However, neurotensin antagonists do not block the c-fos effects of clozapine.

**Clinical pharmacology.** Dr. Tamminga provided an overview of the use of glucose, oxygen (O){superscript}15, and receptor PET imaging techniques for elucidating the pharmacological effects of antipsychotics. Ketamine, a psychomimetic agent and phencyclidine analog, increases blood flow in the temporal, insula, and anterior cingulate cortices and decreases blood flow in the cerebellum. The relationship and time course of blood flow changes in the anterior cingulate and cerebellum differ in patients with schizophrenia and normal controls (Dr. Henry H. Holcomb). In addition, the temporal and insular blood flow changes are correlated with changes in the Brief Psychiatric Rating Scale (Overall and Gorham 1962). These observations suggest a role for these regions in the...
functional neuroanatomy of schizophrenia and positive symptoms. Haloperidol administration is associated with increased glucose metabolism in the basal ganglia and thalamus and decreased metabolism in the inferior and middle prefrontal cortex. These effects raise the possibility that, consistent with the proposition put forth by Dr. Abercombie, the therapeutic action of haloperidol is mediated through basal ganglia–thalamocortical neural circuits, with haloperidol acting at the level of the basal ganglia. By contrast, clozapine has less effect on striatal metabolism than conventional antipsychotics (Dr. Monte Buchsbaum). Preliminary data suggest that sertindole may have an effect on striatal metabolism that differs from haloperidol.

Drs. Marc Laruelle and Alan Breier each presented data on a unique paradigm designed to assess dopaminergic activity in patients with schizophrenia. The procedure is based on the administration of pharmacological agents that alter DA release and the measurement of the subsequent displacement of a radio-labeled DA receptor ligand from postsynaptic DA receptors. Dr. Laruelle reported that amphetamine-induced DA release is elevated in both medicated and unmedicated patients with schizophrenia. Dr. Breier reported a similar finding, with no difference observed in amphetamine-induced DA release between antipsychotic-naïve and chronic patients. In both studies, increased DA release was associated with a transient increase in symptoms. In a preliminary report, Dr. Breier also used the same paradigm to examine the influence of ketamine on DA release. In a group of normal volunteers, ketamine increased DA, but not to the same extent as amphetamine. Dr. Dean F. Wong has also used this paradigm to document increased DA release in patients with schizophrenia. The mechanism underlying the increased DA release is unknown; Dr. C. Benkelfat presented data to suggest that it is not related to increased dopa-decarboxylase activity.

Dr. Paul D. Acton used a multivariate cluster analysis procedure to document increased striatal D2 receptor density, with significant left-right asymmetry, in drug-free male patients with schizophrenia. Dr. Per Karlsson examined D1 receptor concentration in the striatum and neocortex. Although there were no absolute differences in D1 receptor concentrations, antipsychotic-naïve patients with schizophrenia exhibited significantly greater variability in D1 receptor affinity than normal controls.

Dr. Shitij Kapur examined the relative 5-HT2a and D2 receptor occupancy of selected conventional and atypical antipsychotics. Haloperidol was characterized by dose-related D2 occupancy and minimal 5-HT2a occupancy. By contrast, both clozapine and risperidone have greater 5-HT2a than D2 occupancy, with risperidone, but not clozapine, having a similar level of D2 occupancy as haloperidol. The study provides further evidence of the importance of 5-HT2a activity for conferring atypical properties to the newer antipsychotics.

**Clinical trials.** Although there is extensive investigation of new drugs prior to their release onto the market, many questions concerning the comparative efficacy profile of atypical antipsychotics remain. Of particular importance is the efficacy of atypical antipsychotics for treatment-resistant positive and negative symptoms. Dr. Stephen R. Marder presented the results of a 29-week multicenter study examining the efficacy of clozapine and haloperidol. In a replication of earlier studies, clozapine exhibited superior efficacy for positive, hostile, and affective symptoms. However, there was no clozapine/haloperidol difference for negative symptoms. In the same study, Dr. Nina Schooler reported that the majority of patients who responded to clozapine met improvement criteria by week 17, and that over 80 percent of these patients showed some improvement by week 11. Patients who did not show any improvement by week 17 were highly unlikely to ever change. Dr. Robert Rosenheck reported on the 1-year VA Collaborative Study. Clozapine treatment was associated with significantly greater improvement on positive and negative symptoms and on quality of life than haloperidol treatment. However, the negative symptom advantage of clozapine disappeared when the effect of clozapine on EPS was taken into account. In this study, the cost savings for clozapine were accounted for by those patients with severe schizophrenia rather than by the entire study population. This finding is important in light of administrative efforts to curtail injudicious prescription of (costly) novel antipsychotic medications.

Several studies compared the relative efficacy of risperidone to both conventional and atypical antipsychotics. In a carefully designed 8-week double-blind study comparing the efficacy of risperidone and haloperidol, Dr. Donna Ames found that risperidone was associated with greater overall significant improvement, whereas haloperidol was associated with greater use of side-effect medications. Patients had a better subjective response to risperidone. However, this response was more variable than the response to haloperidol, with an increase in both favorable and unfavorable responses and a decrease in neutral responses. Two open-labeled studies examined the comparative efficacy of risperidone and clozapine. Dr. Sean W. Flynn found that clozapine had significant advantages for the treatment of total and positive symptoms and of global measures of functioning. In contrast, Dr. Jean-Pierre Lindenmayer reported no significant differences between the two drugs.

Dr. Gary Tollefson gave an overview of recent studies on the efficacy of olanzapine. In multicenter trials, olanzapine proved superior to haloperidol in overall psychotic...
symptomatology—positive, depressive, and negative symptoms—with a lower propensity to induce EPS and a low rate of "treatment-emergent" tardive dyskinesia (TD) in subsequent long-term studies. It is unclear whether improvement in negative symptoms is due to changes in primary negative symptoms, as suggested by a path analysis, or whether this is confounded by improvements in depressive symptoms and EPS. In a subanalysis of multicenter trial data for patients with their first episode of schizophrenia, olanzapine exhibited therapeutic superiority over haloperidol.

Dr. Tollefson also presented data on a comparative study of olanzapine versus risperidone in schizophrenia. Olanzapine was superior to risperidone in efficacy and had fewer EPS. The mean modal dose was 16.9 mg/day for olanzapine and 7.3 mg/day for risperidone; the dose of risperidone was higher than the current mean modal dose of 4.6 mg/day for risperidone treatment of schizophrenia in the United States.

Olanzapine shares a number of pharmacological properties with clozapine, which suggests that olanzapine may also exhibit superior efficacy for treatment-refractory schizophrenia. However, in a study with treatment-refractory patients, there were no significant differences between olanzapine and chlorpromazine for positive or negative symptoms or for number of patients who met treatment response criteria (Dr. Robert R. Conley).

The use of atypical antipsychotics extends beyond schizophrenia to include affective and other disorders characterized by the presence of positive symptoms and/or behavioral disturbances. Dr. S. Charles Schulz reviewed the use of these agents for such disorders. Their use for bipolar disorder has been most extensively investigated, with the majority of the studies suggesting the efficacy of clozapine and risperidone for this indication.

**New antipsychotic medications.** A second wave of new antipsychotics are currently under various stages of development. Mr. Randall Mack (Abbott Laboratories) gave a progress report on clinical experience with sertindole, which is approved by the FDA and due for release shortly. In multicenter studies, sertindole has been shown to have comparable efficacy to haloperidol but with significantly lower rates of EPS. Mr. Mack emphasized, in the light of recent concerns of cardiotoxicity, the low incidence (<1%) of echocardiogram QTc prolongation during sertindole treatment. There have been no reported instances of torsade de pointes. Dr. Lisa Arvantis (Zeneca Pharmaceuticals) presented an update on quetiapine, another atypical antipsychotic currently under review by the FDA. In short-term clinical trials, quetiapine (at a dose range of 150–750 mg/day) was shown to be superior to placebo and comparable to either haloperidol or chlorpromazine in measures of efficacy. Quetiapine had low rates of EPS and was not associated with dose-dependent increases in EPS. Dr. Edmund Harrigan (Pfizer Pharmaceuticals) described the clinical pharmacology of ziprasidone, an agent that had its New Drug Application filed with the FDA in March 1997 and is currently in phase III clinical trials. Ziprasidone is a potent 5-HT1a agonist and 5-HT2c and 5-HT1b antagonist. It has potent affinity for D3 receptors and moderate affinity for D4 and is a D2-receptor antagonist of comparable affinity to risperidone. It has low affinity for all other receptors, except for modest alpha1 adrenoreceptor antagonism. This profile may account for its favorable side-effect profile, particularly the low potential for orthostatic hypotension. Initial efficacy results are encouraging. Ms. Terri Sebree (Titan Pharmaceuticals) described the clinical pharmacology and initial experience with iloperidone, a promising antipsychotic agent that has just entered phase III clinical trials. Phase II evidence of efficacy was demonstrated at doses of 8 to 16 mg/day with an EPS liability indistinguishable from placebo.

Dr. Pierre Truffinet (Rhône-Poulenc) presented data on fananserin, a selective D2/5-HT1 antagonist whose preclinical studies suggest the potential for antipsychotic efficacy. Jeffrey McKelvy (Trophix Pharmaceuticals) gave an overview of the emerging role for glycine reuptake inhibitors (GRIs) in neurology and their potential as antipsychotic drugs. Type II GRIs are being studied in the treatment of chronic pain and muscle spasticity. Type I GRIs currently under development may have a role in the treatment of schizophrenia based on other evidence (see earlier) of glutamatergic dysfunction in schizophrenia.

**Pharmacology of cognitive impairments.** A number of presentations examined alternative approaches to DA receptor blockade for the treatment of schizophrenia. (-)-3PPP is a partial DA agonist, with 35 percent intrinsic activity at the D2 receptor. (-)-3PPP produces a significant reduction in positive symptoms; however, this effect only persists for 1 week (Dr. Adrienne Lahti).

A large number of studies have demonstrated a disassociation between the effects of conventional antipsychotics on symptoms and cognitive impairments (Dr. Barbara Comblatt). These observations have led to the hypothesis that symptoms and cognitive impairments represent different domains of psychopathology. The advent of atypical antipsychotics, with their novel mechanisms of action, has reawakened interest in the pharmacology of cognitive impairments in schizophrenia and has stimulated the investigation of the potential benefit of atypical antipsychotics on these impairments. Dr. Green reported that risperidone enhanced verbal working memory performance, with the improvement unrelated to change in symptoms. The pharmacological mechanism underlying this improvement is unknown.
A series of studies examined the effect of amphetamine on cognitive functions in patients with schizophrenia and/or related disorders. Dr. Carter found that amphetamine improved selective attention and spatial working memory in patients with schizophrenia, but not in normal controls. Dr. Larry J. Seiver reported similar findings in patients with schizotypal personality disorder. Amphetamine improved the performance of these patients on working memory, executive function, and attention tasks. Dr. Cyril D'Souza examined the effects of ketamine, a noncompetitive NMDA antagonist, on cognitive function in normal subjects. Ketamine induced symptomatic and cognitive disturbances resembling schizophrenia. Glycine, an NMDA agonist, given in low doses attenuated the psychomimetic effects of ketamine.

Dr. Imran B. Chaudhry examined the effect of cyproheptadine, a 5-HT2a and 5-HT2c antagonist, on frontal lobe tasks. Cyproheptadine improved performance on frontal lobe timed or motor tasks. These changes were independent of any effects on symptoms. Dr. John Newcomer compared memory performance in healthy subjects, before and after infusion of insulin. Insulin treatment produced improvement in verbal and spatial memory, which may be related to regulation of cerebral metabolism and/or alteration in serotonergic function. The latter proposition is of interest, given recent observations of glucose and cholesterol dysregulation during treatment with novel antipsychotics that are potent serotonergic antagonists.

Side effects. Compliance with antipsychotics is influenced by both the costs and benefits associated with their use, with side effects being the major cost of these agents. Patients' attitudes toward their medication is significantly associated with compliance (Dr. Stephen Browne). Dr. Thomas Barnes reported that medication noncompliance is common (43% of their sample) even at the first episode of schizophrenia and is related in part to lack of insight. TD is one of the most serious side effects associated with conventional antipsychotic treatment. Dr. Robert S. Goldman reported that poor premorbid scholastic performance and increased cognitive abnormalities at the onset of illness are associated with increased risk of developing TD. Dr. Donald M. Quinlan also noted a relationship between impaired neuropsychological test performance and the development of TD. In addition, he found that patients were most likely to have higher negative symptom scores.

There are no known effective treatments for TD. The association between phenylketonuria and TD suggests that branched chain amino acids, which decrease brain uptake of phenylalanine, may be an effective treatment. In an open-labeled study, 67 percent of the subjects experienced at least a 60 percent reduction in TD. If replicated in controlled studies, this could be of considerable benefit to those patients with persistent TD. Several presentations (Dr. Debra Baisitt, Dr. George Jurjus, Dr. Chand Nair) reported that clozapine is efficacious in controlling severe TD and in tardive dystonia.

A major potential benefit of atypical antipsychotics is a more benign side-effect profile. Dr. William C. Wirshing reported that clozapine is associated with less Parkinsonian and akathisia side effects than haloperidol but that patients were more likely to discontinue clozapine because of intolerance to the drug. Tachycardia, orthostasis, and sedation were the main causes of intolerance to clozapine. Clozapine-induced sedation is more prevalent than recorded in patient charts, and patients do not appear to become tolerant of this effect (Dr. John Lauriello). Dr. Carl H. Miller presented data on the comparative prevalence of EPS among clozapine, risperidone, and conventional antipsychotics. Risperidone was intermediate between clozapine and haloperidol.

A potential complication in the abrupt discontinuation of clozapine is the rapid development of psychotic symptoms. Dr. Steven G. Potkin found no difference after 2 weeks in the reoccurrence of positive symptoms in patients discontinued from clozapine or haloperidol. The probability of relapse in remitted patients, who are rapidly tapered from conventional medications, may be related to the severity of their TD (Dr. Rael D. Strous).

Psychosocial. Patients with schizophrenia are characterized by marked impairments in social and occupational functions. Pharmacological treatments are relatively ineffective in treating these impairments. Therefore, cognitive, behavioral, and other psychosocial approaches have been developed to maximize the level of functioning of patients. Cognitive Adaptation Training (CAT) is a psychosocial approach designed to alter the environment of patients to compensate for their cognitive impairments (Dr. Dawn I. Velligan). CAT has been shown to significantly improve the adaptive function of both inpatients and outpatients. Cognitive behavior therapy programs specifically designed to meet the residential, vocational, and recreational needs of patients may be more effective than general social skills training programs (Dr. Volker Roder).

There is relatively little empirical information on the cognitive processes predictive of vocational outcome. Dr. James M. Gold found that patients with poor vocational outcome have impaired neuropsychological performance, whereas patients with either good or poor outcome perform badly on cognitive tasks (e.g., degraded stimulus version of the Continuous Performance Test) that are putative vulnerability markers. These results suggest that there may be cognitive processes that are uniquely associ-
ated with disability and are superimposed on vulnerability or illness-related cognitive impairments.

A major new direction in the treatment of schizophrenia is the development of early detection and intervention programs. These programs are based on the proposition that early intensive treatment may minimize the morbidity and functional disabilities associated with the illness and enhance quality of life (Dr. Stephen Browne). The latter result contrasts with observations from more chronic populations, where service utilization is relatively unrelated to subjective quality of life (Dr. Jack E. Scott). Dr. Patrick D. McGorry presented the results examining the efficacy of cognitively oriented psychotherapy for early psychosis (COPE). Patients who received COPE had fewer positive and negative symptoms and were more likely to have integrated their psychotic experience into their lives, but they were more likely to exhibit various forms of affective and somatic symptoms. Early intervention may also lead to decreased relapse rates, with the efficacy of the intervention related to the level of familial expressed emotion. Essential components of early intervention services are client engagement, activity coordination, and service collaboration (Dr. Elizabeth A. Spencer).

Most early intervention programs offer family psychosocial services, and their efficacy provides further support for the importance of these services. However, Medicare, Medicaid, and patient interview data suggest that family treatments are still either unavailable or underutilized (Dr. Lisa Dixon).

Summary

The 1997 International Congress on Schizophrenia Research was the largest ever, with the vast number of presentations reflecting the success of the effort to bring schizophrenia research into the forefront of neuropsychiatry research. The body of work presented at this year's Congress also reflects the complexity of the disorder and the diversity and creativity of the multitude of scientists striving to unravel its etiology, pathophysiology, psychology, and pharmacology. The conference was impressive not only for the huge increase in attendance since the last biannual meeting, but particularly for the breadth and depth of scientific presentation. The conference was noteworthy for the consolidation of earlier research trends such as the notion of neural dysconnectivity in schizophrenia, the potential of genetics and pharmacogenetics, and the emerging viewpoint that progressive neurodegenerative brain changes may, in some cases, be superimposed on a neurodevelopmental pathology. The progress in pharmacotherapy and the rapidity with which new and diverse antipsychotic medications are coming on line could hardly go unnoticed. At the same time, studies of service utilization, practice recommendations, supportive psychotherapy, and early intervention strategies in schizophrenia served to remind participants of the need for comprehensive approaches to the care of patients with this disabling disorder.

References


Acknowledgments

ICOSR Young Investigator Awardees

Katherine J. Aitchison, MRCPsych
Section Clinical Neuropharmacology
Department of Psychological Medicine
Institute of Psychiatry
London, UK

Donna Ames, M.D.
West Los Angeles Veterans Affairs Medical Center
Los Angeles, CA

Deanna M. Barch, Ph.D.
Western Psychiatric Institute and Clinic
Pittsburgh, PA

Sally A. Berry, M.D., Ph.D.
Department of Psychiatry
Case Western Reserve University
Cleveland, OH
Frances Yee, Ph.D.
Department of Pediatric Infectious Disease
John Hopkins University School of Medicine
Baltimore, MD

The Authors
Robert W. Buchanan, M.D., is Professor of Psychiatry, University of Maryland School of Medicine, and Chief, Outpatient Research Program, Maryland Psychiatric Research Center, Baltimore, MD. Peter F. Buckley, M.D., is Associate Professor of Psychiatry, and Medical Director, Northcoast Behavioral Healthcare System. Carol A. Tamminga, M.D., is Professor of Psychiatry, Maryland Psychiatric Research Center, Baltimore, MD. S. Charles Schulz, M.D., is Professor and Chairman, Case Western Reserve University, Cleveland, OH.

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