

MODULE 2: PATHOPHYSIOLOGICAL MECHANISMS

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1. EPIDEMIOLOGY

Psychiatric epidemiology studies the distribution of disorders in well-defined populations. Its goal is to identify risk factors that explain why some populations are at higher risk for psychiatric illness than others. To attain this goal it asks three fundamental questions: 1) How many people from a well-defined population will be diagnosed with an illness at a specified point or period in time? (i.e., what is the prevalence?) 2) How many people from the population will onset with the illness during a specified period of time? (i.e., what is the incidence?) and 3) What proportion of the population will develop the disorder at some time during their entire lifetime (i.e., what is the lifetime prevalence?).

Prevalence Rate

The prevalence rate of a disorder is the number of people diagnosed with the disorder divided by the total number of persons examined in the population under study. The computed rate depends on several factors: the definition of the disorder, the total number examined in the population, and the method used to choose who to examine. Ideally, the sample used to compute prevalence should be representative of the population as a whole.

Epidemiologists usually report the prevalence rate as the number of cases per 1,000 people surveyed within a year. This is called the one-year prevalence per 1,000. Many studies of schizophrenia from around the world have found these rates to range from a low of 0.6 per 1,000 to a high of 17 per 1,000. Most studies find rates between 3 and 10 per 1,000.

The prevalence rates for schizophrenia do not depend on any obvious demographic differences between countries. Whether we consider East versus West, developed countries versus less developed countries, or other classifications, the one-year prevalence of schizophrenia is approximately 0.5 percent. That is, schizophrenia will be found in approximately one half of one percent of the population at any point in time. The highest prevalence (17 per 1,000) was reported from a Swedish sample in 1978. The population studied lived in northern Sweden; it is isolated from the rest of the country and located in a bleak, austere environment. The high prevalence there might indicate that such environments are suitable, and even attractive, for the socially withdrawn and isolated lifestyle of many schizophrenic patients.

Incidence Rate

Another way of reporting the rate of schizophrenia in a population is to estimate the number of new cases to appear in the population during a specified period of time; this is called the incidence rate. Prevalence rates (as discussed above) include both new and old cases because once schizophrenia has emerged it usually runs a chronic, unremitting course. Thus, once patients are classified as schizophrenic, they usually remain schizophrenic. One problem facing incidence studies of schizophrenia is how to define onset. In many cases the onset of illness is slow, starting with subtle signs of social withdrawal and unusual thinking or behavior. Because the time of onset is difficult to determine, reported incidence rates are usually based on a patient's first visit to psychiatric services for schizophrenic symptoms.

The incidence rate is usually expressed as the number of new cases in a given period per 100,000 population. For schizophrenia incidence rates range from a low of .10 to a high of .70. As was the case with the prevalence figures, the incidence of schizophrenia is not highly variable over time or across geographical areas.

Lifetime Risk

Most people suffering from schizophrenia first develop the illness during the adolescent or early adult years. The “age at risk” period for schizophrenia is between approximately 16 and 39. Men tend to be younger at the time of onset compared with women. Due to the variability of age at onset, prevalence and incidence rates will vary according to the age and sex composition of the population studied. The age distribution is particularly important when estimating the probability or risk of a person becoming schizophrenic throughout his or her lifetime. We call this the lifetime risk. To estimate lifetime risk, the age distribution of the population surveyed should be taken into account. A variety of statistical methods are available for this purpose.

The lifetime risk for schizophrenia ranges from 0.3 to 3.7 percent, depending on the definition of schizophrenia and the method of survey used. Taken together, studies of the lifetime risk for schizophrenia in the general population suggest that it is around one percent. In other words, approximately one in every hundred people will develop a schizophrenic disorder at some time in their life.

Risk Factors

Schizophrenia has been found in all cultures through the world. Paradoxically, it persists in the population despite decreased fertility (i.e., the majority of people with schizophrenia do not have children, due to the various social handicaps that the disease produces). When differences between countries have been observed, these are usually due to diagnostic differences, not differences in true rates of illness. For example, in the 1960s a team of American and British researchers set out to determine why the hospital incidence of schizophrenia in the United States significantly exceeded that of Great Britain (28.0 vs. 17.9 per 100,000 population). In British Hospitals, mood disorders were diagnosed much more often than in American hospitals (36 vs. 7 per 100,000). The U.S.-U.K. project was begun to determine the source of these differences. This project showed that when identical methods of diagnosis and assessment were used, the incidence of schizophrenia did not differ significantly between American and British hospitals.

Epidemiological studies have found that schizophrenic patients usually belong to lower socioeconomic groups. Since low social class is associated with many disadvantages such as poor nutrition and limited access to health care, researchers set out to determine if economic deprivation increased the risk for schizophrenia. This work suggests that the excess of schizophrenics in the lowest socioeconomic group is a result—not a cause—of schizophrenia. Since the disease hampers educational and occupational attainment, schizophrenic patients born to high social class families tend to fall in social status and those born into economic hardship seldom escape it. Several studies have found that the social class distribution of the parents of people with schizophrenia does not differ from that of the general population. Male patients tend to have lower job achievement than do fathers, brothers, and other male relatives. Whereas fathers tend to rise in job status, schizophrenic sons tend to fall into jobs of lower and lower status or become disabled. Thus, it appears that, although low socioeconomic status is known to have deleterious effects, it is primarily an effect of schizophrenia rather than its cause.

Gender differences in schizophrenia have received a good deal of attention. Among schizophrenics, men have an earlier age at onset and poorer premorbid history. They also have more negative symptoms, a poorer outcome, and more structural brain abnormalities as measured with neuroimaging tools. Women are more likely to display affective symptoms, paranoia and auditory hallucinations. They are less likely to have the negative symptoms of schizophrenia.

The gender differences in symptomatology make it difficult to determine if rates of the disorder vary by gender. Recent studies indicate a higher incidence for males than females. There also appears to be a higher prevalence among males.

2. GENETICS

Work in psychiatric genetics tends to follow a logical series of questions ordered as follows:

1) Is the disorder familial? 2) What are the relative contributions of genetic and environmental factors to disease mechanisms? 3) What is the mode of transmission in families? 4) Where is the gene located? 5) How is the gene expressed? 6) What are its functions and products? 7) What role do those products play in an illness? This section will update students about developments that seek to answer these questions for psychiatric disorders.

Methods Applied

Studies of psychiatric genetics have historically used a group of specific methods to explore the answers to these questions. These methods include family history studies, family studies, twin studies, adoption studies, linkage studies based on familial aggregation of markers, and techniques applying the methods of molecular biology to establish linkage, search for candidate genes, and determine the molecular mechanisms of the disorder. Among these methods the family history techniques were among the earliest and most primitive. Nevertheless, these techniques, combined with family and twin studies, have established the importance of genetic factors in the transmission of schizophrenia.

Because it is relatively easy to implement, the family study is usually the first line of investigation for psychiatric genetic research. Ideally, such studies should use the blind case-control paradigm. The cases (subjects with the disorder) and controls (subjects without the disorder) used in genetic studies are known as probands. Following the selection of cases and controls, the study attempts to assess the diagnostic status of as many of the relatives of cases and controls as possible. The aim is to compare rates of illness in relatives of cases to rates in the relatives of controls. If a disorder has a genetic etiology, then relatives of ill probands should carry a greater risk for the illness than relatives of controls. In addition, the risk to relatives of probands should be correlated with their degree of relationship to the proband, or the amount of genes they share in common. If genes cause schizophrenia, then siblings of schizophrenic probands should be more likely to have schizophrenia than cousins of the probands.

However, because familial transmission can also be caused by environmental influences, inferences from family studies are limited. Solid evidence for genetic influence comes from twin, adoption and linkage studies. Identical or monozygotic (MZ) twins inherit identical chromosomes and thereby have 100% of their genes in common. In contrast, the genetic similarity of fraternal or dizygotic (DZ) twins is no different than that of siblings. On average, DZ twins share 50% of their genes. Thus, MZ and DZ twins are markedly different with regard to their genetic similarity. However, if twin pairs are reared together then the degree of environmental similarity between MZ twins should be no different than that between DZ twins. In the twin method, any differences between a pair of MZ twins are assumed to be due primarily to environmental influences. In contrast, differences between DZ twins could be due to either genetic or environmental influences. Thus, comparing the co-occurrence of a psychiatric disorder in the two types of twins provides information about the relative contributions of genetic and environmental factors in the etiology of the disorder.

Adoption also creates a useful paradigm for psychiatric genetic studies. Children adopted at an early age have a genetic relationship to their biological parents and an environmental relationship to their adopted parents. Thus, adoption studies can determine if biological or adoptive relationships account for the familial transmission of disorders. If genes are important, then the familial transmission of illness should occur in the biological, but not the adoptive family. In contrast, if culture, social learning or other sources of environmental transmission cause illness, then familial transmission of illness should occur in the adoptive, but not the biological family.

Family History and Family Studies

In 1982 Gottesman and Shields reviewed the studies of morbid risk for schizophrenia among relatives of schizophrenic probands. Averaging over the accumulated studies, they found a risk to parents of 5.6%, a risk to siblings of 10.1%, and a risk to offspring of 12.8%. The risk to parents is reduced because they are selected for having reproduced and the presence of schizophrenia has an adverse effect on the probability of reproducing. The risks to second-degree relatives range from 4.2% for half-siblings to 2.4% for uncles and aunts. First cousins, a type of third-degree relative, have an average risk of 2.4%.

When a rigorous methodological approach is utilized, a substantial majority of recent studies provide evidence for the familial transmission of schizophrenia. Although the absolute rates of schizophrenia among relatives of schizophrenics tends to be lower than that reported in the earlier studies, due to the restrictiveness of contemporary definitions of schizophrenia, the risk to relatives compared to that of controls has remained quite consistent.

The data reported by Gottesman and Shields had been collected by the pioneering studies of schizophrenia that had been completed prior to the development of standardized criterion-based diagnostic algorithms. However, modern studies using more rigorous research methods and narrower, criterion-based definitions of schizophrenia are also consistent with the genetic hypothesis. In these studies, the rate of schizophrenia in first-degree relatives of schizophrenic probands is about 4% compared to less than 1% in controls. Diagnostic practices probably account for the lower rates observed in contemporary studies. The risk to first degree relatives increases to about 8% when the

schizophrenia category is broadened to include atypical schizophrenics. Thus the risk figures for schizophrenia based on contemporary criteria are similar to the figures obtained by the earlier European studies when atypical cases are included.

Twin Studies

If schizophrenia were due entirely to genetic factors, the concordance rates for monozygotic twins and dizygotic twin pairs would be 100 percent and 50 percent, respectively. Evidence for a strong genetic component to schizophrenia would be given by a significantly higher concordance rate for schizophrenia in monozygotic twin pairs than in dizygotic twin pairs.

In a summary study, Kendler pooled the results of nine twin studies of schizophrenia. Overall, about 53 percent for monozygotic twin pairs were concordant for schizophrenia, compared with 15 percent of dizygotic twin pairs. These data suggested that approximately 70% of the liability to schizophrenia was due to genetic factors. Notably, the concordance rate for monozygotic twin pairs was not 100 percent. This indicates that environmental factors also play a crucial role in the etiology of schizophrenia. However, it is interesting to note that in general mental illnesses may have a stronger genetic component than “physical” illnesses. Overall, disorders such as schizophrenia, autism, and Alzheimer’s disease have higher MZ:DZ ratios than general medical disorders such as breast cancer, hypertension, or ischemic heart disease.

Adoption Studies

The observation that relatives of schizophrenics have an elevated risk for schizophrenia compared to controls is consistent with theories of both genetic and environmental transmission. Adoption studies offer an opportunity to unconfound genes and environment. Heston reported a morbid risk for schizophrenia of 16.6% among 47 adopted-away offspring of schizophrenic mothers, compared to 0% among 50 adopted controls. This finding, which has been replicated by others, suggests that it is the genes provided by one’s parents rather than the environment that are most important in imparting risk for schizophrenia.

Kety and a group of collaborators carried out extensive adoption studies of schizophrenia using case registry data available in Denmark (the Danish Adoption Study). He and his colleagues examined the biological and adoptive relatives of schizophrenic and non-schizophrenic adoptees. Twenty-one percent of the biological relatives of schizophrenic adoptees had schizophrenia or a related disorder. In contrast only 11 percent of the biological relatives of non-schizophrenics had schizophrenia or a related disorder. The adoptive relatives of the schizophrenic and non-schizophrenic adoptees did not differ in rates of schizophrenia. Kety and his colleagues also studied children born to schizophrenic parents who had been adopted by non-schizophrenic parents. These were compared with the biological children of non-schizophrenic parents who were adopted by non-schizophrenic parents. Schizophrenia and related disorders were found in 32 percent of the former group but only in 18 percent of the latter group. These researchers also studied children who had been born of non-schizophrenic parents but raised by a schizophrenic parent. They found that rearing by a schizophrenic parent did not predict schizophrenia in children who were not genetically predisposed to the disorder.

The Mode of Transmission

Classic Mendelian models of inheritance cannot adequately describe the genetic transmission of the disorder. For example, if schizophrenia were caused by a fully penetrant dominant gene, then 50% of the offspring of one schizophrenic parent should be schizophrenic, but the observed value is much lower. If schizophrenia were caused by a fully penetrant recessive gene, we would expect 100% of children with two schizophrenic parents to be schizophrenic. The observed value is 36.6%. Clearly, more complex models are needed to describe the genetic transmission of schizophrenia. Quantitative or mathematical modeling studies provide a strategy for doing so.

Single major locus models (SMLs) propose that the pair of genes present at a single locus account for the transmission of schizophrenia. Overall, segregation analyses do not support the SML model of inheritance for schizophrenia. All studies that have applied statistical tests of the degree of segregation have rejected the SML model. The failure to find a SML model that unequivocally accounts for the familial transmission of schizophrenia led to the testing of polygenic models. These models assume that more than one gene causes the familial pattern of the disorder. Oligogenic models propose a relatively small number of loci. In contrast, multi-factorial polygenic (MFP) models propose a large unspecified number of loci. Simulation studies have suggested that multi-locus models including gene

interactions may be needed to account for the familial pattern of illness in schizophrenia. There is some evidence favoring a multi-factorial polygenic etiology for schizophrenia (MFP). In particular, MFP segregation analysis studies suggest that multi-factorial polygenic factors account for 60% to 70% of the familial pattern of schizophrenia. These results cannot rule out, however, the possibility of a mixed model in which an SML component and a MFP component both exist.

Approaches Based on Molecular Biology

During recent years, the traditional approaches to studying the genetics of schizophrenia have been complemented by the new perspectives of molecular biology. Essentially, as the concepts of molecular genetics and molecular biology have been integrated into the study of complex human illnesses such as schizophrenia, a new way of thinking about their genetics has emerged. In the 21st century, people no longer think of genes as static or simple phenomena. Instead, they recognize that genes interact dynamically with one another and with their cellular and extracellular components to regulate body and brain functions. Instead of maintaining a static blueprint, genes turn on and off (i.e., “are expressed”). Investigators now recognize that the regulation of expression may be as important a contributor to disease risk as genes alone.

Although there is probably no single “correct” definition of a gene, from the perspective of molecular genetics a gene is defined as a section of DNA that codes for the RNA that produces protein products. In addition, regulatory genes are also present. Regulatory genes determine when proteins will be produced, thereby controlling the process of gene expression. Gene expression occurs when genes are turned on or become active. Because of this dynamic view of gene function, investigators have begun to talk about “disease risk genes” rather than genes that simply “cause” a disease. These “disease risk genes” are conceptualized as genes that contain a variation in DNA that leads to a change in gene function that in turn contributes to the development of a disease.

From the perspective of modern molecular genetics, multiple steps are required in order to achieve a complete understanding of disease genes. (These steps do not necessarily occur in the logical chronological order in which they are described.) One step, which has conventionally been conceptualized as the first step, involves finding or locating a specific disease gene. Techniques such as linkage, described below, are the traditional approaches. Once a gene has been identified, it is then cloned for use in subsequent research. Cloning, once a difficult process, has now become relatively simple as a consequence of technological advances. Subsequently, investigators must sequence the gene in order to identify its component base pairs. Other aspects of understanding genes are disciplines referred to as “functional genomics” and “proteomics.” During this phase, investigators identify the product of the gene and its function. Understanding the function often involves determining how a given protein interacts structurally and functionally with other systems, such as second messenger systems in the central nervous system. Finally, in order to understand disease genes, investigators must identify how DNA variation in the gene contributes to the development of the disease.

Linkage Analysis

Rapid developments in the laboratory science of molecular genetics during recent years have made it possible for schizophrenia researchers to use better methodologies for finding genes. Linkage analysis is one example of these methods. Linkage analysis capitalizes on the crossing over of chromosomes that occurs during meiosis. Due to crossing over, chromosomes in an offspring are not identical to any of the original chromosomes of its parents. When gametes are formed, the original chromosomes in each parent's pair cross over each other and exchange portions of their genetic material. After multiple crossovers, the resulting two chromosomes each consist of a new combination of genes. In addition to the physical distance between loci, the number of crossovers that occurs between them will determine whether or not they will recombine. An odd number will result in recombination, whereas an even number will not. If two loci are very far apart, the probability of an odd number of crossovers between them is equal to the probability of an even number. As a result, the probability of recombination is 50%. Therefore, genes on the same chromosome that are very far apart from one another are transmitted independently, as are genes on different chromosomes. Linkage occurs when two genes on the same original chromosome are so close to each other that crossing over rarely or never occurs between them. Closely linked genes usually remain together on the same chromosome after crossing over. Thus, if two genes are closely linked, then they will be transmitted together within families.

Linkage analysis (also referred to as reverse genetics, because it assumes no prior knowledge of the disease mechanism) determines if a putative disease gene is closely linked to a known genetic

marker (a measurable human trait controlled by a single gene with a known chromosomal location). Linkage analysis became a powerful tool when molecular geneticists developed methods to define DNA markers throughout the genome. A DNA marker is defined by laboratory techniques that can identify specific nucleotide sequences at specified chromosomal loci. The traditional method used to identify disease genes has been positional cloning, an approach that begins with linkage studies that seek to detect chromosomal susceptibility loci (regions harboring disease genes).

Linkage studies of schizophrenia have been inconclusive. Numerous linkage studies have now been performed in schizophrenia, with chromosomes 1q21-q22, 6q21-q22, 8q21-q22 emerging with perhaps the strongest evidence for linkage. Linkage studies have, however, been plagued with problems of nonreplication. It may be that previous attempts to detect linkage to schizophrenia have failed due to the use of relatively small samples. It is difficult to determine exactly how many pedigrees of what size would be needed to detect linkage, but there is a consensus in the literature that the detection of schizophrenia genes will require very large samples. If schizophrenia is genetically heterogeneous (as seems likely), elucidating the genetic mechanisms will be very challenging.

Candidate Gene Approaches

An alternative approach to linkage studies are the candidate gene approaches, also sometimes referred to as “forward genetics.” The term “forward” is used because investigators begin their search using candidate genes that have already been identified (e.g., the gene controlling nerve growth factor). Candidate genes are chosen because they are hypothesized to be related to the disease mechanism. In candidate gene studies done to date, genes commonly chosen include those that control neurotransmitters or neuroreceptors, or that serve as regulators of brain development. These genes can then be studied in affected families, using statistical methods that determine whether the candidate gene occurs more commonly in individuals with the illness as compared to those from control families. Another application of candidate gene approaches involves the use of transgenic mice, in which candidate genes have been either introduced or over-expressed (“the knock-out mouse” or the “knock-in mouse”). While appealing because it is hypothesis driven, the candidate gene approach is handicapped by the large number of possible candidates that can be studied.

Advances Associated with The Human Genome Project: The Genetics of Complex Illnesses

Investigators interested in the genetics of schizophrenia are hopeful that the fruits of The Human Genome Project will provide substantial leverage for future searches for disease genes. This project has provided a reference sequence of three billion base pairs. It has also identified important markers of genetic diversity that may have relevance for finding disease markers: single nucleotide polymorphisms (SNPs, or “snips”). Snips are mutations in a single nucleotide, which may be associated with the predisposition to a given disease. One of the best-known snips that has been identified to date is the APO ϵ 4 allele. The APO ϵ 2 allele has been shown to be a protective factor for Alzheimer’s Disease, while the APO ϵ 4 predisposes to its development. This example illustrates a pattern that is likely to characterize much of modern genetics, including the genetics of schizophrenia. The APO ϵ 4 Allele is a disease risk factor, but the gene cannot be said to “cause” the disease. Rather, it increases risk in conjunction with a variety of predisposing factors, such as co-existing cardiovascular disease, history of head injury or lower educational levels.

Snips occur as a consequence of mutations, again indicating that genetic material is dynamic rather than static. It is now recognized that mutations occur spontaneously in the process of DNA replication. They may also be induced by exogenous sources, such as exposure to radiation. Mutations probably occur quite frequently, and most are eliminated as soon as they occur by checking mechanisms within the cell. Some may persist, however, and some of those that persist may lead in turn to disease (e.g., cancer, which has an increased risk in individuals who have a higher rate of exposure to radiation).

In the 21st century world of genetics the traditional dichotomy between genes and environment, which provided a philosophical framework for twin and adoption studies for many years, is now perceived as a false dichotomy. We now know that environmental factors influence genes in a variety of ways – mutations, the effects of stress, the effects of endocrine regulation, or the introduction of viruses into cellular machinery. The elimination of this false dichotomy creates both complexities and opportunities. We now recognize that genes only lay out a blueprint. The DNA in every cell in the body is the same. The process of gene expression leads to both cell differentiation and to the development of diseases. Depending on which genes are “turned on” or expressed, a cell will develop into a liver cell or a brain cell. Also depending on whether a gene is expressed or not, a gene may contribute to the development of a

disease process. The recognition of this false dichotomy provides hope because it suggests that we can potentially prevent diseases before they occur by stopping the expression of “bad genes.”

The modern conceptualization of the genetics of schizophrenia groups it among the “complex illnesses,” which include various forms of cancer, hypertension, diabetes, and many kinds of mental illness. These genetically complex illnesses are probably all caused by multiple genes, each of which has a small effect. In a given individual a genetic predisposition may be present, but it does not lead to the development of an illness unless the predisposition is released by a variety of non-genetic triggers. Examples of relevant triggers for schizophrenia include a difficult maternal labor, infections, subtle brain injuries, or exposure to toxins such as amphetamines. For the development of most complex illnesses, including schizophrenia, “multiple hits” are probably required. In the case of schizophrenia hits that affect adolescent brain development may be the most important.

The Definition of the Phenotype

Most investigators agree that, despite the wonders of modern molecular genetics and molecular biology, perhaps the most pressing problem that we face in applying these technologies is knowing how to define the disease phenotype. Our current definitions of the phenotype of schizophrenia simply represent a clinical consensus, which was derived primarily in order to improve diagnostic reliability. The clinician-scientists who have been involved in the DSM or ICD definitions did not define the phenotype with the goal of identifying disease mechanisms. Therefore, in the context of identifying the molecular and cellular processes that lead to an illness such as schizophrenia, it is important to revisit a fundamental clinical question: how do we define the phenotype? There are several different kinds of answers to this question. They include the use of clinical symptoms, its characteristic course and outcome, its array of cognitive deficits, or the search for endophenotypic markers.

The search for endophenotypic markers is currently a cutting-edge issue in the study of the mechanisms of schizophrenia. Investigators are hopeful that they may be able to find markers that are closer to the disease mechanism than the relatively superficial symptoms traditionally used to define a given illness. In the case of schizophrenia, some candidate markers that are currently discussed include eye tracking abnormalities, impairments in prepulse inhibition, abnormalities in backward masking, or various measures of motor or mental coordination. Some of these potential markers are discussed later in the sections on neurophysiology and neuroimaging.

As they search for markers, investigators must also frequently ask themselves what the putative marker actually marks. Is it an indicator of vulnerability to develop the disorder? Of sub-threshold forms of the disorder? Of the endophenotype (which may or may not be expressed as illness)? Or the expressed phenotype? At present, no consensus exists to provide an answer to these questions.

3. NEUROPATHOLOGY

The neuropathology of most psychiatric diseases always has been more problematic than the pathomorphology of neurological diseases. With the exception of general paresis, the dementias, and the psychiatric syndromes that are secondary to neurological or medical disorders (e.g., traumatic brain injuries, systemic lupus erythematosus), no obvious and homogeneous types of brain pathology have yet been detected for the major psychiatric illnesses such as schizophrenia or manic depressive illness. Affective disorders, which are believed by many psychiatrists to be caused by deficits or functional imbalances of neurotransmitter systems, have never gained much interest from neuropathologists. Schizophrenia, however, was in the first half of the century the subject of some 200 pathoanatomical studies. These studies were initiated by many of the Founding Fathers of modern psychiatry, who were also neuropathologists, such as Kraepelin, Brodmann, Alzheimer, Nissl, and the Vogts. Their unsuccessful search for brain abnormalities in this disease was subsequently followed by several decades of silence. The death of the neuropathology of schizophrenia was announced approximately 40 years ago by neurologist Fred Plum, who commented that, “Schizophrenia is the graveyard of neuropathology.” During the past twenty years, however, study of the neuropathology of schizophrenia has reemerged to become one of the outstanding challenges of current psychiatric research.

There are several possible explanations for the present lack of an obvious and homogenous brain pathology in major psychiatric disorders. Like genetics, neuropathology suffers from “the problem of defining the phenotype.” One explanation is that most psychiatric diseases, as classified in ICD or DSM, are not discrete disease entities with a single identifiable pathophysiology, but rather are diagnostic constructs that provide a useful conceptual shorthand to permit communication between clinicians;

according to this explanation, the etiology and pathophysiology are likely to be as unhomogenous as are the clinical symptoms. Even if the symptoms are similar, different etiologies could lead to them. Alternatively, it is conceivable that the brains of many patients suffering from psychiatric disorders are anatomically normal, and that their psychopathology is caused solely by functional disturbances of neurotransmitter or other neurochemical systems that are reversible, without accompanying pathoanatomical alterations. Yet another explanation is that possible morphological changes in typical psychiatric diseases are so subtle that they have escaped traditional neuropathological assessment methods, which have been based mainly on qualitative tissue assessment. Yet another possibility is that the changes are in brain areas that have not yet been examined by pathologists. There is now evidence that the anatomical anomalies in at least a substantial subgroup of schizophrenics are localized in brain systems for which the functional significance became known only recently and therefore were overlooked in the first half of this century. The best example is the limbic system, the function of which was fully recognized in 1952. Another explanation is that some disorders, and especially schizophrenia, are due to disordered connectivity (either functional or anatomical or both); this disordered connectivity occurs between regions and will not be found by looking in a single region using traditional tools of neuropathology.

The introduction of neuroimaging techniques has provided neuropathology with a strong complementary tool to assist in studying the neuropathology of schizophrenia. Magnetic Resonance (MR) imaging has shown that subgroups of patients suffering from schizophrenia have structural anomalies outside the range of healthy control subjects, in addition to demonstrating statistically different group means between patients and normal control subjects. Usually, however, in the majority of the patients the changes are subtle and not comparable in severity or extent to the changes seen in the degenerative brain diseases.

Methodological Problems

Much of the controversy that previously characterized the neuropathology of schizophrenia was due in part to methodological flaws associated with qualitative postmortem brain tissue assessment without statistical evaluation. If diagnostic constructs such as schizophrenia and affective disorders are composed of various clinical and biological subtypes, large samples of patients would be necessary to obtain representative data by which subgroups can be characterized morphologically. Possible methodological errors involve brain changes secondary to neurological or vascular diseases, pre-agonal conditions such as protracted coma, chronic diseases of peripheral organs, paraneoplastic limbic encephalopathia, drugs known to affect brain structures (e.g. cortisol), possible effects of psychoactive medications, time to fixation, and postmortem shrinkage and swelling of brain tissue.

Neuropathological Studies in Brains of Schizophrenics

A new era of neuroanatomical schizophrenia research started about twenty years ago. During that time, some fifty neuroanatomical postmortem studies in schizophrenia were published. The majority of these studies demonstrated various types of subtle anomalies in limbic structures, i.e., hippocampal formation, parahippocampal and cingulate gyrus, entorhinal cortex, amygdala and septum. These structures play a crucial role in the functions that are now thought to be disturbed in schizophrenia (i.e. the coordination of cognitive and emotional activities, the higher cortical integration and association of different sensory modalities, representation and analysis of environmental contexts, sensory gating, and the neuronal generation and control of basic drives and emotions). Therefore, a broad spectrum of schizophrenic symptoms might be related to structural and functional disturbances of limbic brain regions.

The findings in the limbic system comprise (1) reduced volumes and cross sectional areas of hippocampus, parahippocampal gyrus and amygdala; (2) enlargement of adjoining parts of the ventricular system (temporal horn) especially in the left hemisphere, (3) reduced cell numbers and cell size in the hippocampus, parahippocampal gyrus, and entorhinal cortex; (4) reductions of white matter tracts which contain myelinated fibers traveling to and from the hippocampus, parahippocampal gyrus and entorhinal cortex; (5) disturbed cytoarchitecture and fiber architecture, as well as abnormal cell arrangements in the hippocampus, cingulate gyrus, entorhinal cortex, frontal and temporal cortical areas; (6) deficits in small (probably inhibitory) interneurons in the cingulate gyrus and (7) an increased incidence of a cavum in the septum pellucidum.

Although the type and extent of the reported changes varies and some of the findings could not be replicated by all research groups, and although there seems not to be a homogenous pattern of limbic pathology in schizophrenia, the vast majority of the studies completed to date agree that there are subtle

changes in limbic brain regions in a significant percentage of schizophrenics. The magnitude of the pathology is far less than that seen in the classic degenerative brain diseases, such as Alzheimer's and Pick's disease. Limbic tissue volumes, cell numbers and size differ by some 10-30 percent between schizophrenics and controls. There is a considerable overlap between patients and controls, with only about one quarter of the patients having values outside the normal range. Direct evidence linking temporolimbic pathology to schizophrenic symptoms has been provided by neuroimaging studies using computed tomography, magnetic resonance imaging and positron emission tomography. According to these studies, there may also be an association between left temporolimbic pathology and some of the positive symptoms of schizophrenia.

There are also reports of changes in brain regions outside the limbic system. Two areas that have aroused strong interest during recent years are the thalamus and the prefrontal cortex. Multiple studies have now demonstrated abnormalities in cell density and size in the medial dorsal nucleus of the thalamus; this nucleus is of interest in schizophrenia because it projects to the frontal cortex. In addition, other investigators have examined prefrontal cortex and have found abnormalities in cytoarchitecture. It now appears that changes in this region are not due to cell loss, but rather to changes in dendrites or spines on cells, as manifested by cortical thinning secondary to loss of neuropil. These observations are consistent with neurodevelopmental theories of schizophrenia.

A key question about the pathophysiology of schizophrenia is whether the disease is due to a neurodegenerative or a neurodevelopmental process. In a recent article, Bogerts and colleagues reviewed the neuropathological studies which addressed this question. They found 27 postmortem studies published in the last 20 years that are consistent with a disorder of brain development, eight studies consistent with a disorder of an inflammatory or degenerative brain disease, and 14 studies with no comment on the etiology of the disease. Neuropathological strategies to approach etiological considerations include (1) investigations of glial cells, (2) examination of the cortical architecture, and (3) studies of cerebral asymmetries. The majority of the glial cell studies in schizophrenics seem to indicate that the anatomical abnormalities described in the mesotemporal structures (cingulate gyrus and thalamus) are not associated with gliosis, and therefore might reflect a disorder of brain development.

The findings of abnormal architectonic features of single nerve cells, cell clusters, cortical layers and myelinated fibers in limbic structures, as well the increased incidence of a cavum septi in schizophrenics, are strong indicators of a disturbance of brain development. However, the reported cytoarchitectural abnormalities are subtle, and they are not comparable in extent or severity with the well-known disorders of cortical development. There is a substantial overlap to similar developmental irregularities in normal controls, even if the group means differ significantly.

4. NEUROIMAGING

Neuroimaging, also referred to as brain imaging, comprises a group of related techniques that permit clinicians and research scientists to directly visualize brain structure and function in living human beings. Two of the major techniques are used primarily to visualize brain structure: computerized tomography (CT) and magnetic resonance (MR). Two others permit the study of physiologic and biochemical functions: single photon emission computed tomography (SPECT) and positron emission tomography (PET). The oldest of these techniques, CT, has been available since the 1970s. The other three entered the neuroimaging repertoire in the 1980s. An adaptation of MR to measure cerebral blood flow was developed in the 1990s and led to a new and powerful tool for functional imaging (fMR). Although initial applications of neuroimaging were often in neurology and neurosurgery, psychiatrists have become steadily more aware of the importance of these techniques for the study of mental illness as well, and all are now firmly established as part of the psychiatric repertoire.

Neuroimaging techniques have broadened the clinical and scientific domain of psychiatry. Neuroimaging has become the major method by which psychiatrists can approach the basic neuroscience dimension of their field. Its technology has given them the opportunity to directly study brain structure and activity, providing many new applications in order to define and map the nature of normal brain function and to determine how it is disturbed in patients suffering from mental illness. Each of the neuroimaging techniques is complementary to the others, since each contributes a particular kind of information and has its own inherent strengths and limitations.

Basic Principles of Neuroimaging

CT images, the oldest of the imaging tools, are generated by passing an x-ray beam through the head and measuring its degree of attenuation. Cerebrospinal fluid (CSF), bone, and brain tissue vary in their ability to attenuate x-rays, with bone producing the greatest attenuation and CSF the least. The degree of attenuation is picked up by detectors on the opposite side and mapped on a slice by slice basis; each slice is subdivided into a grid of tiny cubes (referred to as "volume elements" or "voxels"), and the extent of attenuation within each of these voxels can be measured numerically as a "tissue density number." The term "tomography" within computerized tomography refers to the fact that the brain is sliced, while the "computed" term refers to the fact that high speed computers are needed to collect information concerning the large quantity of numbers generated and to turn all this information into a picture, which visually displays the degree of x-ray attenuation within each tiny chunk of tissue. The density numbers are converted to a greyscale value, with low numbers (i.e., CSF) coded as black and high numbers (i.e., bone) coded as white. When the numbers are displayed visually, they are referred to as "picture elements" or "pixels." The overall grey scale map becomes the now widely familiar pictures generated by a CT scanner. A variety of reconstruction and filtering techniques are applied to smooth the boundaries between pixels and make the picture more visually appealing. A steady technological progression has occurred since the original development of clinical CT; early scans produced six slices and took 35 minutes, while current scanners can potentially produce numerous slices and scan the brain in seconds or even milliseconds.

The basic principles involved in CT are applicable to all the other neuroimaging techniques. All depend on the principle of generating slices, collecting information from a grid of voxels, and using high speed computers and filtering techniques in order to produce a visual image that is a dot matrix of pixels. The major difference between CT, MR, SPECT, and PET is "what goes in." For CT, an x-ray beam is attenuated. For MR, the hydrogen protons in the brain are perturbed by being placed in a magnetic field, and subsequently their rate of return to their original condition ("relaxation time") is measured. For SPECT and PET, radioactive tracers are injected, localized in particular brain regions on the basis of physiologic or biochemical activity, and the number of counts in the site of localization or uptake is measured. The various differences between CT, MR, SPECT, and PET turn on how these different "input factors" affect the information that can be derived. In general, MR, SPECT, and PET are far more complex than CT, since they are measuring processes that are more complicated than the simple attenuation of an x-ray beam.

Magnetic resonance has only been available since the mid-1980s. Unlike the CT signal, which has a single component, the MR signal is produced by three different components. The MR signal is produced by placing the patient's head in a relatively high field strength magnetic field (typically 1.5 tesla in most current imaging equipment), which has the effect of concentrating the magnetic moment produced by the individual protons in the tissue so that it is large enough to be measurable; the net magnetic moment can then be deflected or tipped by sending radio frequency signals that excite the tissue and change the magnetic moment of the hydrogen protons. After excitation, the protons slowly relax and return to their original position. The MR signal is produced through a combination of the density of the hydrogen protons and the two different components of relaxation, known as T1 and T2. The timing of the excitations (or pulse sequences) can be selected in order to vary the relative contribution of the three components of the MR signal.

The appearance MR scans and the information that they provide will vary, depending on the weighting of the three components of the MR signal. The **proton density** (PD) image produces similar color shadings for CSF and white matter and makes grey matter relatively bright; the **T1 weighted** (T1) image shows the best tissue discrimination, with CSF being very dark, grey matter lighter but in a grey tone, and white matter appearing relatively light; the **T2 weighted** (T2) image makes CSF bright and has the poorest discrimination between grey and white matter. Not only do these different types of scanning sequences produce a different grey scale for the different tissue types, but they also have a different value for identifying pathological tissue. For example, T2 weighted sequences are particularly good for identifying regions of tissue pathology such as multiple sclerosis plaques or areas of infarction, which tend to produce a relatively bright signal in a T2 weighted sequence. The pulse sequence variables that are manipulated to produce these different types of images are known as the echo time (TE) and the repetition time (TR). A short TE and a long TR produce a proton density image; a short TE and a short TR produce a T1 weighted image; and a long TE and long TR produce a T2 weighted image. The interrelationships between TE, TR, and the three components of the MR signal can be summarized schematically.

The type of scanning sequence will typically vary, depending on the question that is being asked. In general, if the goal is to obtain excellent grey/white/CSF discrimination and to visualize anatomy well, a T1 weighted sequence will be chosen. If the goal is to identify areas of tissue pathology, a T2 weighted sequence will be chosen. The plane of section for MR is also under operator control and can be transaxial, coronal, or sagittal. Sometimes several different scanning sequences will be chosen.

Because of its flexibility and power, MR is steadily surpassing CT as a structural imaging technique. The strengths and limitations of these two structural techniques are different. MR does not involve the use of any ionizing radiation and is therefore considered to be a relatively safe procedure; as a consequence, it is particularly desirable for the evaluation of children; CT, on the other hand, does involve radiation exposure. CT has no other major risks, however, and is relatively comfortable for the patient, while some patients experience claustrophobia during an MR scan because they must be placed inside a relatively long tunnel and have a limited visual field due to the magnetic coil that surrounds their head. While the tissue resolution of CT has improved steadily, it is poor compared with MR. The one tissue that CT visualizes well is bone, which cannot be seen at all with MR (although the bone marrow is visualized). CT slice planes are currently limited to transaxial views, while MR can slice in any plane and currently can also produce a three dimensional acquisition as well as a 3D reconstruction.

Studies of schizophrenia have clearly demonstrated the power and flexibility of structural imaging techniques to go beyond the mere visualization of brain abnormalities and to use these techniques as scientific probes in order to explore disease progression and the mechanisms that may contribute to its onset. A variety of brain abnormalities have been described in schizophrenia, including ventricular enlargement, sulcal enlargement, decreased cerebral size, and a reduction in size of brain subregions such as the hippocampus, temporal lobes, or frontal lobes.

The earliest imaging studies of schizophrenia used CT scanning, beginning with the pioneering work of the Northwick Park group under the leadership of Tim Crowe. They demonstrated that a relatively older chronically hospitalized group of patients displayed ventricular enlargement. While these findings were initially questioned because of the nature of the sample, they have now become the most replicated result in modern psychiatric research. More than 50 CT studies have been done, and approximately 80 percent have shown that schizophrenics as a group have enlarged ventricles when compared to control subjects. Most CT studies have measured ventricular size using a single slice, typically one which passes through the body of the lateral ventricular system, and generated a ratio of ventricle to brain size, based on the outline of the cerebrum on the same slice (ventricular: brain ratio, or VBR). This measure has provided a relatively crude way of controlling for individual differences in head size.

Most recent studies of ventricular enlargement have employed MR, which provides multiple slices through the ventricular system at a relatively high level of resolution, thereby permitting reliable measurements of ventricular volume. MR scanning permits powerful three-dimensional visualization of both internal brain structures and brain surface anatomy. The illustrative slide, based on measurement of ventricles, hippocampus, and brain surface in an individual with schizophrenia and a healthy volunteer demonstrates the advantages of MR for visualization and measurement. In general, MR studies with these methodological refinements have continued to support the finding of ventricular enlargement in schizophrenia.

The emphasis in schizophrenia research has shifted almost completely to the use of magnetic resonance imaging to study structural abnormalities in schizophrenia. The technology of MR has advanced rapidly, and equipment is available in many centers around the world that permits the relatively rapid acquisition of thin slices (in the range of 1.5 mm) through the entire brain. In many research centers, multiple sequences are collected using a combination of T1-weighted, T2-weighted, and PD images, which can be co-registered and superimposed. This combined use of multiple sequences as "multispectral or multimodal imaging." The high quality and high-resolution images that are produced through the use of modern MR technology permits a variety of volumetric and other measurements that were not previously possible.

The speed with which structural MR technology has advanced creates challenges. The opportunity to visualize many aspects of the brain in exquisite detail leads to a desire to measure them quantitatively. Research using MR began using the same manual approaches that were initially used in CT – visually identifying and tracing around the boundary of regions or structures such as the ventricles. It quickly became apparent, however, that more automated approaches were needed, and consequently several centers have worked intensively on developing new tools for image analysis.

Perhaps the most widely used tool is known as “segmentation.” Segmentation has several different meanings. At its simplest, it refers to the identification of the boundaries of a region, and in this sense it could be either manual or automated. Frequently, however, the term “segmentation” is used to refer to what is more properly known as “tissue classification.” Particularly when multi-spectral approaches are used, automated methods can be used to classify brain tissue into grey matter, white matter, and CSF. The simplest way to “segment,” or classify tissue, is to create a histogram of signal intensity numbers for individual voxels and use this as a guide for identifying the intensity value that indicates a cutoff between the three kinds of tissue. The histograms are not necessarily clean or simple, however, and therefore more complex multispectral approaches are considered preferable. Tissue classification is also complicated by a problem that permeates all of neuroimaging, a phenomenon known as “partial voluming.” This term refers to the fact that a given voxel may contain two different kinds of tissue (e.g., 25% grey matter and 75% white matter in a voxel on the boundary between the cortical rim and incoming axons), and the signal intensity in that voxel will therefore represent an average of the two tissue types. This problem can be partly addressed by weighting the amount of tissue in a given voxel and producing images that are “continuous” rather than “discrete” or categorical. Partial voluming is one of several phenomena that make high quality tissue classification more difficult. Another is movement of the patient during image acquisition, which produces a blurring of boundaries known as “movement artifact.” When multispectral sequences are used, however, the increased information produced through multiple sequences can produce images of the boundaries between grey matter, white matter, and CSF that looks strikingly similar to postmortem tissue and are based on more sophisticated statistical approaches to tissue classification than simple histogram delineation (e.g., the use of discriminate analysis techniques. Furthermore, slice thickness can be reduced to as thin as .5 mm, producing images with striking anatomic accuracy.

Another technique for image analysis that is enjoying increasingly wide use is known as “voxel averaging,” or voxel-based morphometry (VBM). This technique, pioneered by Alan Evans in Montreal and first applied to the study of schizophrenia by Nancy Andreasen, requires that images from a group of similar individuals be transformed into the same space. Such transformations are sometimes referred to as “spatial normalization.” “Morphing” or “warping” are other terms that are used to refer to this process, which can use either linear or non-linear methods to create the spatial transformation. Once the images are “in the same space,” they can be averaged voxel by voxel in order to produce a “composite brain.” The composite images can be whatever groups a person wishes to compare: e.g., a group of patients with schizophrenia versus a group of healthy volunteers, or a group of healthy women versus healthy men. The two groups can then be subtracted from one another and their differences displayed in a difference map, using some sort of statistical technique such as an affect size. Andreasen first applied this method to the study of schizophrenia, identifying differences in the thalamus and in white matter tracts projecting to the frontal lobes. Tools for doing voxel averaging are now provided in the widely used image-analysis package developed by Karl Friston and other members of the London team led by Richard Frackowiak, known as statistic parametric mapping (SPM). While the ease with which voxel averaging can be used to make group comparisons is tempting, it can also be fraught with a variety of problems, such as artifacts produced by partial voluming or spatial normalization.

While early CT studies emphasized the measurement of ventricles, increased prominence of cortical sulci was also evident. MR provides opportunities to visualize sulci and gyral patterns in detail and to measure them. This opportunity leads in turn to the possibility of studying individual differences in gyrification, the relationship between gyrification and brain development, and gyrification in schizophrenia. Karl Zilles and his team in Germany have studied gyrification across human age ranges and have shown that it undergoes progressive changes. The fetal brain is essentially smooth (lissencephalic) until about the sixth month of fetal life, when the primary sulci begin to emerge (e.g., the Sylvian fissure). Thereafter, the brain continues to steadily grow and expand within the cranial vault, crumpling in the process to produce the secondary and tertiary sulci. There are substantial individual differences in patterns of gyrification, which probably reflect a variety of both genetic and non-genetic influences. These facts suggest that the opportunity to visualize and measure gyrification with MR can address a number of questions about normal brain development and abnormalities that may arise in a disease such as schizophrenia. Because of the technical difficulties in producing accurate automated images of the cortical surface that can be precisely measured, gyrification studies have only been completed very recently. The Iowa group has developed methods to reconstruct brain surface features automatically and to generate a variety of measures, such as surface area, sulcal and gyral curvature indices, and measures of cortical thickness. These studies have demonstrated abnormalities in

childhood schizophrenia and first episode schizophrenia. They have indicated that patients with schizophrenia have decreased cortical thickness, widening of sulci, and narrowing of gyri—all findings that are consistent with other imaging or neuropathological studies. Further, these abnormalities are observed in very young patients and during the early stages of the illness, an observation that is consistent with a neurodevelopmental pathophysiology.

MR can also be used to measure a variety of brain subregions. The ability to visualize sulcal landmarks such as the central sulcus or Sylvian fissure has led to many investigations that subdivide the brain into its four lobes: frontal, temporal, parietal, and occipital. When combined with stereotactic systems such as the Talairach Atlas, lobe measurements can be generated automatically. Various cortical and subcortical subregions have also been measured in a variety of MR studies, such as the superior temporal gyrus, the planum temporale, caudate, putamen, and hippocampus. All these structures are relatively easy to visualize with MR. Others are more difficult, including thalamus and amygdala, either because they do not have distinct boundaries or because they contain a mixture of grey and white matter. Increasingly, however, even these more “difficult” structures are being measured precisely with MR technology. If measurements are to be accurate, however, painstaking care must be given to demonstrating that the measurements are both reliable and valid.

MR studies have now produced a variety of findings concerning brain abnormalities in schizophrenia. None has been replicated with perfect consistency, but many have been supported by several studies. The inconsistency in the literature is probably reflective at least in part of variability in imaging technology, measurement techniques, and patients across sites. Some of the more consistently reported abnormalities include decreased temporal lobe size, decreased size of the superior temporal gyrus, decreased hippocampal size, decreased thalamic size, decreased frontal size, and regional decreases in grey matter volume. All of these decreases must be interpreted within the context of a generalized decrease in brain size, accompanied by an increase in CSF within the ventricles and on the surface of the brain. The generalized decrease in brain size, perhaps the most widely replicated finding in schizophrenia research, requires that measurement of subregions be “corrected” in some way to insure that they do not simply reflect this generalized reduction. The most common method for correction is either closely matching groups on gender and height. Other correction techniques include co-varying for height (particularly in groups with disproportionate representation of men and women) or co-varying for overall brain size.

A number of investigators have attempted to determine whether these regional abnormalities have a relationship with clinical presentation. The literature contains conflicting results in this area as well, but some trends do emerge. Perhaps the most consistent relationships are between structural abnormalities and cognitive impairment. A relationship between decreased size in the superior temporal gyrus and auditory hallucinations has also been widely reported. The occurrence of thought disorder and decreased size of the planum temporale may also occur, as may a relationship between decreased frontal lobe size and negative symptoms.

One group of studies has examined indicators of neurodevelopmental abnormalities in schizophrenia. This possibility has been partially buttressed by a variety of findings. A number of investigators have reported finding an increased rate of midline neurodevelopmental defects in schizophrenia, including cavum septi pellucidi and partial or complete agenesis of the corpus callosum. In addition, investigators have observed that patients with schizophrenia may have a decrease in cerebral or intracranial volume. Skull growth is largely determined by brain growth; in human beings, cranial growth is partially fixed by the closure of the sutures at approximately two years of age and nearly complete by the age of six. Decreased cranial size in schizophrenia suggests that an abnormality in neurodevelopment has occurred that has slowed the process of brain growth. These findings have triggered an interest in the various types of processes that could produce a neurodevelopmental arrest or injury, including genetic factors, nutrition, toxins, viruses, and obstetrical complications.

The combination of structural imaging techniques and the twin paradigm has added a fascinating dimension to these findings. The twin paradigm was initially used in a CT study conducted by the Reveleys and collaborators in Great Britain. The study examined seven discordant monozygotic twins and a group of normal dizygotic and monozygotic twins. Using VBR as a measure, they found a high level of heritability in ventricular size in the normal twins. In addition, ventricular size was slightly greater in the dizygotic normals than in the monozygotic normals and had a lower degree of heritability, as would be predicted genetically. In the discordant pairs, the twin who had schizophrenia had significantly larger ventricles than his co-twin, as well as significantly larger ventricles than the normal monozygotic twins. A somewhat surprising finding, however, was the fact that the well co-twin also had ventricular enlargement

when compared to the monozygotic normals. This study has been introverted as suggesting that a genetic (and potentially neurodevelopmental) factor contributes to ventricular enlargement in both twins in the pair. However, some sort of non-genetic injury may have occurred in addition to the underlying genetic factor, which produced additional ventricular enlargement and also led to the development of schizophrenia. These findings are consistent with the “multiple hit” theory of schizophrenia.

The team based at NIMH, led by Daniel Weinberger, has reported a very similar finding using MR. In this study, the effected twin could be distinguished from the ill twin in 12 of the 15 pairs. In addition to ventricular enlargement, sulcal enlargement, and increased hippocampal size were also reported.

Another interesting finding that has emerged consistently from the MR literature has been an increase in basal ganglia size in patients with schizophrenia who have been chronically treated with typical neuroleptic medications. The early reports of this finding interpreted as due to a failure in pruning. More recently, however, evidence seems to point to the role of neuroleptic treatment instead. This phenomenon has been interpreted as arising from neuropil proliferation in response to chronic D2 receptor blockade, an observation that has been supported by functional imaging studies that indicate typical neuroleptic treatment produces dramatic increases in blood flow in the basal ganglia. When patients treated with a typical neuroleptic are switched to an atypical, the caudate and/or putamen then decrease to normal size. Early studies that use structural imaging tools were based on the assumption that medications could not induce structural changes in the brain. These studies of caudate and putamen size have sounded a warning that this assumption does not hold true and that medications can produce measurable changes in structures in the brain, which is much more “plastic” than was initially believed.

Functional Imaging Techniques

In addition to the extensive work conducted with CT and structural magnetic resonance, many neuroimaging tools have become available to permit the study of brain function. Collectively, these are referred to as “functional imaging techniques.” These tools include single photon emission computer tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance (fMR). The major application of these tools for the study of schizophrenia has been to visualize the working mind while it conducts mental activity. Most of these techniques create this visualization by measuring cerebral blood flow or metabolism.

Single Photon Emission Computed Tomography (SPECT)

The first study to examine cerebral blood flow was conducted by Seymour Kety in the mid 20th century. Kety did prescient and pioneering studies comparing global blood flow in a group of patients with schizophrenia and a group of control subjects. Although he found no group differences, he predicted that differences would indeed be found when the capacity was developed to measure regional blood flow, rather than global blood flow, as was done in his study.

The earliest studies of schizophrenia using the technology of SPECT, which permits regional evaluations, were conducted as early as the 1970s and 1980s. A pioneering study was conducted by David Ingvar and Neils Lassen. They examined regional blood flow in a group of patients with schizophrenia as compared to normal controls. They noted a decrease in blood flow in the prefrontal cortex and described this abnormality as “hypofrontality.” In addition, they noted that the phenomenon of hypofrontality was more severe in patients who had prominent negative symptoms. These results were of great interest, since negative symptoms represent a loss or diminution of mental functions that we know to be performed by the prefrontal cortex, such as fluency of thought and speech, forming emotional attachments, formulating social and moral judgments, volition and drive, planning and identifying goals, and formulating abstract concepts. The use of SPECT was subsequently continued by an NIMH team led by Daniel Weinberger and Karen Berman. While Ingvar and Lassen studied the “resting brain,” Weinberger and his group examined mental activity using a task selected because it had been shown in neuropsychology to tap frontal functions. Specifically, they selected the Wisconsin Card Sorting Task (described below) and compared it with a number matching task in a group of patients and controls. The patients had lower blood flow in the prefrontal cortex during both tasks, but the differences were particularly striking for the Wisconsin Card Sorting Task (WCST). While the healthy volunteers produced robust frontal activation while performing the WCST, the patients were markedly hypofrontal.

SPECT studies involve a relatively crude technology and have now largely been supplanted by either positron emission tomography (PET) or functional magnetic resonance (fMR).

Positron Emission Tomography (PET)

PET is distinguished from SPECT in a variety of ways. The tracers used in SPECT emit single photons (hence, single photon emission computed tomography), while the tracers for PET are positron emitters. In both cases, the tracer is taken up in brain tissue, and the imaging process generates a picture of its regional distribution, thereby providing an index of blood flow/metabolic activity/ chemical activity. The images derived from positron emitting tracers are, however, based on the detection of two photons rather than a single photon; when the positron is emitted in tissue in the brain, it collides with an electron, and both are annihilated, producing two 511 keV photons in the process. These photons are detected by scintillation detectors surrounding the brain in a ring configuration. Because the "two point coincidence line" generated by the pair of photons provides a more precise technique for localizing activity, the resolution of PET is greater than that of SPECT.

PET, however, is quite costly. It requires the availability of an on site cyclotron to generate the positron emitting tracers, a highly specialized tomograph dedicated solely to PET imaging, a well-equipped radiochemistry lab in which tracers can be synthesized on site, and an experienced team of physicists and radiochemists. On the other hand, PET has enormous power and flexibility because of its relatively high resolution, its capacity for quantification, and its adaptability to a broad range of imaging paradigms.

Early PET studies used fluorodeoxyglucose (FDG), and these early studies also supported the concept of hypofrontality. The FDG method was supplanted in the early 1980s by the use of $^{15}\text{OH}_2\text{O}$ method. While FDG required the study of long time windows (up to an hour), the "water method" permits short sequential snapshots of mental activity using time windows that can range from 10 to 120 seconds. Typically, a PET "water study" uses four to eight injections that differ subtly from one another and thereby permit the serial dissection of cognitive operations involved in related tasks.

An extensive number of PET and fMR studies have been used to examine brain function in schizophrenia during the past decade. While early studies used relatively simple tasks and just a few standard paradigms, the more recent work has been characterized by the examination of multiple brain systems and careful consideration of a variety of confounds, such as the effects of treatment, chronicity, or symptomatology. The accompanying slides illustrate some of this work. For example, memory has been an important emphasis in PET studies. Typically, these studies have collected a group of healthy, normal volunteers and identified the functional circuitry used in a given task in the normal brain. For example, when remembering a group of well-learned words normal subjects show increased blood flow in the frontal operculum, the thalamus, and the cerebellum. When given the identical task, patients fail to activate most of these regions, despite the fact that they are performing the task as well as the normal volunteers. In addition to failing to activate the normal circuits, they actually show decreased flow in the frontal lobes.

A series of slides are provided, which are drawn from the work of Andreasen, Paradiso, and Crespo-Facorro, which illustrate how a somewhat more complex paradigm can be used in PET studies to examine a single symptom that is common in schizophrenia. In this study, the Iowa team examined blood flow during a visual stimulus that evoked an emotional response. They compared the cerebral blood flow patterns that occur when the brain responds to pleasant versus unpleasant emotional stimuli. In normals, the two types of stimuli were compared by subtraction, with the areas of increased blood flow during the unpleasant images shown in red, while the areas of increased flow during the pleasant images are shown in blue. Unpleasant activations included extrastriate visual cortex, cerebellum, and amygdala. Pleasant activations were almost totally in the frontal lobe, including medial, orbitofrontal, and dorsal lateral frontal cortex. Therefore, healthy normals appear to activate higher cortical regions (i.e., frontal regions) while looking at pleasant images during an emotion attribution task, while they use the classic danger recognition region (i.e., the amygdala) during the unpleasant images.

Subsequently, a sample of medication free patients with schizophrenia were collected and compared to the healthy volunteers using the same paradigm. The two groups were compared with a nonparametric statistical technique known as randomization. In these images, the areas where flow was decreased during the unpleasant stimuli are shown in blue, whereas areas where flow was increased during the unpleasant stimuli are shown in red. (These analyses emphasize the response to the unpleasant images because the patients showed no activations at all in response to the pleasant images). Areas of decreased flow included the thalamus, extrastriate visual cortex, and hippocampus, while areas of increased flow included the insula, putamen/nucleus accumbens, and superior frontal regions. As in the "remembering words" study described above, the patients performed the unpleasant

emotion task normally, in that they gave the same readings to the unpleasant pictures that the normals did.

PET studies have now been used to examine multiple different cognitive systems in schizophrenia. Examples include studies of attention, facial recognition, and various forms of memory. Abnormalities in frontal function are relatively consistent across studies, as are abnormalities in temporal lobe function. In addition, some surprising areas have emerged with considerable consistency, such as the thalamus and cerebellum. These studies continue to be supportive of the concept that schizophrenia is not a disease of a single brain region, but rather affects distributed circuitry throughout the brain.

In addition to studies of the change in brain activity during the performance of a mental task, other investigators have used functional imaging to examine the relationship between brain blood flow and symptomatology. An important study from Cornell in the United States and the British group at Queen's Square examined brain regions activated while patients were hallucinating and found increased activity in multiple regions, including temporal lobes, auditory cortex, and thalamus. Other studies have noted a relationship between negative symptoms and decreased frontal blood flow. Liddle and colleagues have also shown a relationship between several different specific brain regions (i.e., left and right frontal, temporal) and the three dimensions of psychopathology that have emerged from recent studies of the interrelationships between the diverse symptoms of schizophrenia (i.e., negative symptoms, disorganization, and psychoticism).

Functional Magnetic Resonance (fMR)

Functional magnetic resonance (fMR) is the newest of the imaging technologies to become widely available. Because it uses standard equipment, does not require the synthesis of isotopes, and does not lead to exposure to ionizing radiation, fMR has become the fastest growing field in neuroimaging. Conceptually, fMR is based on the fact that the conversion of hemoglobin to deoxyhemoglobin produces an endogenous paramagnetic tracer that is an index of cerebral blood flow and that can be measured using standard MR equipment. The signal generated is referred to as the BOLD (Blood Oxygenation Level Dependent) signal. The earliest studies focused on simple paradigms, such as the delivery of visual stimuli, which should predictably activate the visual cortex and in fact did. Subsequently, investigators turned to more complex mental activity. This step was taken with some trepidation, since the BOLD signal is much weaker than the signal measured with PET, and initially there was some concern that fMR could not be used to measure distributed circuits or complex higher mental tasks. Verbal fluency was one of the first tasks to be examined. Investigators indeed found that during a verbal fluency task, normal subjects activated dorsal lateral prefrontal cortex, as well as temporal and parietal regions. Patients with schizophrenia, on the other hand, failed to activate these regions or activated them much less.

As fMR has matured, increasingly complicated and sophisticated tasks are being applied. One widely used example is the "N-Back task," a widely used test of working memory. Many fMR studies uses a "boxcar" design, during which an experimental task (e.g., an N-Back task) is compared with a resting baseline in alternating blocks that may last from 10 to 20 seconds. The example on the slide illustrates a "2-back" task (in which the subject is instructed to remember a designated probe and then press a button when that probe reappears.) In the 2-back version of this task, the subject has to remember the stimulus with only one intervening distractor. (In a longer and more difficult 3-back or 4-back task, the distractor number would be appropriately increased.) In the comparison task, the subject is simply instructed to monitor for a specific target and press a button when he sees it. As this example illustrates, all aspects of the task are controlled except for the experimental condition itself. The 2-back task in normals has been shown to activate multiple distributed circuits in the brain, including bilateral dorsolateral frontal cortex, bilateral parietal regions, and the anterior cingulate. When the 2-back task is given to unmedicated patients with schizophrenia, blood flow is markedly decreased or absent in the regions used by normals. Only one small activation is present in the anterior cingulate, an important attention region in the brain.

5. NEUROPSYCHOLOGY/COGNITIVE PSYCHOLOGY/COGNITIVE NEUROSCIENCE

What is Neuropsychology?

There is ample evidence, much of which has been reviewed in the previous sections, that the bizarre experiences and behavior that define schizophrenia are associated with structural and functional

brain abnormalities. The task of neuropsychology is to demonstrate the precise relationship between mental processes and brain function. This task is especially challenging in the case of schizophrenia.

Classical Neuropsychology

The main body of neuropsychological knowledge is derived from the study of neurological patients with brain lesions with a known and circumscribed location. From studies of such patients, large numbers of psychological tests have been developed which are sensitive to lesions in particular brain areas. These tests cannot be used in isolation. Typically a circumscribed brain lesion leads to an abnormal pattern of test performance, with the majority of tasks being performed normally, while a small subset are performed very abnormally. The pattern of test performance can be used to predict the site of the lesion. For example, a patient with medial temporal lobe damage might be found to be amnesic, with grossly impaired performance on memory tests, while his performance on IQ tests remains at a normal premorbid level.

Cognitive Neuropsychology/Cognitive Neuroscience

Cognitive neuropsychology, which is closely linked to cognitive neuroscience, emphasizes cognitive processes (mental functions) rather than test performance or lesion location. Psychological tests are used to try to identify, as precisely as possible, the cognitive processes that are impaired in a brain damaged patient. For example, a typical amnesic patient will have impaired *episodic memory* (what happened yesterday), while *semantic memory* (knowing what words mean), *working memory* (remembering a telephone number for a few seconds), and *procedural memory* (being able to ride a bicycle) remain intact. There is particular interest in studying dissociations between processes (i.e., patient A is impaired on episodic memory and not procedural memory, while patient B shows the reverse pattern). It is believed that identification of such dissociations will enable us to discover the fundamental cognitive 'modules' upon which mental function depends. It is also believed that these cognitive modules will map onto discrete brain systems. It is recognized that performance on psychological tests will always depend on a number of cognitive functions. Thus, cognitive impairments must be inferred from the pattern of performance across a number of tests.

Neuropsychology and Schizophrenia: Methodological Issues

The Schizophrenia Lesion

A somewhat naive approach to the neuropsychology of schizophrenia would be to apply a battery of neuropsychological tests to a large group of carefully diagnosed patients and then to infer from the pattern of performance that there was a lesion in a particular location. This approach assumes that schizophrenic patients are like patients with discrete lesions in an unknown location, but this of course is not the case. We know from the direct studies of the brain reviewed above that schizophrenic patients do not have discrete localized lesions. Indeed, many people believe that the brain abnormality is caused neither by a lesion nor by degeneration, but rather reflects abnormal development. We have very little information about the relationship between performance on psychological tests and developmental brain abnormalities.

Drugs and Institutionalization

Even if we cannot infer where the 'schizophrenia lesion' is from the pattern of test performance, information concerning test performance is important for characterizing the cognitive impairments associated with schizophrenia. However, there are further problems of interpretation that must be resolved before this exercise can be completed. The majority of patients with schizophrenia are heavily medicated during their first breakdown and often remain on medication for the rest of their lives. In addition to neuroleptics, patients often receive anticholinergic drugs to combat the motor side effects of the neuroleptics and may also receive benzodiazepines to combat sleep disturbances. All these drugs may well impair performance on psychological tests. For example, there is evidence that anticholinergics and benzodiazepines impair the acquisition of memory. Evidence about the effects of neuroleptic drugs on cognition is much less clear. For obvious reasons, there are no studies of the effects of long-term neuroleptic medication on normal volunteers. Studies of such effects in schizophrenic patients are confounded by the effects of neuroleptic medication on symptomatology. In the acute phase of the illness, a patient is likely to perform better after treatment than before, because of the reduction in the severity of symptoms.

Before the advent of "care in the community," schizophrenic patients remained in the hospital for very long periods (20-30 years). For a time it was widely believed that cognitive impairments could be caused by this 'institutionalization.' There is evidence that if patients are moved from an impoverished to an enriched environment, their scores on IQ tests will increase. However, more recent studies show that patients cared for in the community can also show cognitive impairments. Clearly the cognitive impairments observed in some schizophrenic patients cannot be solely attributed to institutionalization.

Specific and Nonspecific Impairments

It is well known that schizophrenic patients are likely to perform almost any psychological test badly. A general impairment across a wide range of tests is very uninformative from a neuropsychological point of view. Localization of lesions depends upon identification of impairments in one cognitive domain while others remain intact. IQ tests are designed to measure general levels of cognitive performance. Thus, by matching groups on IQ, there is a better chance of identifying specific areas of impairment.

Subgroups

In addition to showing impairments on tests, schizophrenic patients characteristically show very variable performance on tests; some patients perform well while others perform very badly. Given this heterogeneity, the mean performance of a large group is not very representative. A great many studies have tried to identify homogeneous subgroups. This grouping is usually based upon symptomatology. For example, a number of studies have contrasted patients with *negative features* with patients with *positive symptoms*. In many cases it has been observed that the patients with negative features show more marked cognitive impairments. There are many practical and theoretical advantages to be gained from contrasting subgroups of patients. First, it is relatively easy to match subgroups of schizophrenia for background variables such as drug treatment and hospitalization. On the other hand, it is impossible to find "normal" controls who are matched in this way. Second, if a particular pattern of test performance is found to be associated with a subgroup of patients defined in terms of either cross-sectional or persistent symptomatology, this pattern will have implications about the psychological processes that underlie the symptomatology. An alternative approach to looking at subgroups of patients involves looking at subgroups of symptoms (i.e., dimensions of psychopathology, as described in module one).

The Neuropsychology of Schizophrenia: Findings

Laterality

A number of authors have suggested that the pattern of impairments on neuropsychological tests is consistent with damage to the left hemisphere. A specific problem with language tasks would point in this direction. However, other (but fewer) authors have proposed that the right hemisphere is damaged. They cite evidence such as specific difficulty with face processing and problems with nonverbal aspects of speech such as prosody, which are supposedly subserved by the right hemisphere. Yet other authors have suggested that the problem lies in the communication between hemispheres, citing similarities between schizophrenic patients and "split-brain" patients. The evidence is in favor of any of these various hypotheses remains weak. A major problem is the lack of agreement between neuropsychologists on the precise nature of the differences between cognitive processes in the two hemispheres.

Lobology

There is probably more agreement about the function of the different lobes of the brain than there is concerning differences between left and right hemispheres. There is some agreement that tests sensitive to posterior damage are less impaired in schizophrenia than those sensitive to anterior damage. Thus, few studies have claimed evidence of occipital damage in schizophrenia, some have claimed evidence of parietal damage, many have claimed evidence of temporal damage, and even more have claimed evidence of frontal damage. This evidence is best discussed in terms of the cognitive functions associated with these various brain areas.

Cognitive Studies: Faculties

Attention

The poor performance shown by schizophrenic patients on neuropsychological tasks is frequently ascribed to a disorder of "attention." However, attention comes in many varieties, and each variety has many components. Attempts to specify precisely which aspect of attention is impaired have not been entirely successful. Broadly speaking, schizophrenic patients seem to be most impaired in 'controlled' or 'voluntary' aspects of attention. They are unable to sustain attention in vigilance tasks; they have difficulty in attending to one source of information rather than another (being particularly prone to the effects of distraction); and they have particular difficulty in withholding inappropriate responses. The problem with these results is that none is specific to schizophrenia. Furthermore, the pattern of impairment across tests of attention can be described in terms of difficulty, i.e., the schizophrenic patients perform worse on the more difficult tasks. Thus, defects of attention may well be part of an undifferentiated cognitive impairment.

Memory

There is increasing interest in memory processes in schizophrenia. Patients can be found who have memory problems sufficient to claim that they are suffering from amnesia. In general, and as with attention, schizophrenic patients tend to be impaired on more difficult memory tasks that required active processing of material. Thus, they are more impaired on recall than on recognition, and they tend not to organize random lists of material. On the other hand, procedural and semantic memory probably remain largely intact.

Language

There is little evidence that schizophrenic patients have any problems with the understanding of language. Rather, the problems lie with the difficulties that other people have in understanding what the patients are saying. Studies of language production in schizophrenia suggest that the lower levels of processing remain largely intact. Thus, phonology, semantics and syntax are usually normal. Abnormalities appear at higher levels such as those involved in discourse planning and the use of language for communication. These problems will be discussed in more detail in the section on social interaction. There is some evidence that the more chronic or "negative" patients show evidence of reduced complexity of syntax in their speech.

Executive Processes

A current popular model of psychological function proposes that there are several cognitive modules that can function more or less independently of one another. These subserve many functions, including aspects of perception, attention, memory, and language. The use of these modules and the coordination of their function is controlled by a higher level system (or systems), variously referred to as the "central executive" and the "supervisory attentional system." It will have been clear from our survey of cognitive abnormalities in schizophrenia that most of their problems could be ascribed to this high level system.

Models of Signs and Symptoms

A relatively new approach to the study of schizophrenia is sometimes labeled *cognitive neuropsychiatry*. This approach attempts to explain particular signs and symptoms, rather than schizophrenia in general, in terms of neuropsychology.

Negative Features

Many surveys of current mental state in schizophrenic patients have shown that they often have negative features, such as poverty of speech, flattening of affect and psychomotor retardation. These signs bear a striking resemblance of the behavior seen in some neurological patients after damage to the frontal lobes. The essential similarity lies in the lack of spontaneous behavior or "will," which Kraepelin considered to be a fundamental aspect of the disorder. Patients with these signs tend to perform especially badly on "frontal" tests. A similar pattern of behavior is also seen in some patients with Parkinson's disease, which is associated with damage in the striatum. There are major anatomical connections between frontal cortex and the striatum, which have been described as 'functional loops.' It is therefore plausible that the negative features of schizophrenia are associated with a frontostriatal dysfunction. The specific pathology will be different from that associated with frontal lesions or Parkinson's disease, but the effect is on the same cortical-subcortical circuitry.

Positive Features

Hallucinations and Delusions

Hallucinations are the most characteristic psychotic symptoms. Such symptoms are rarely seen in patients with neurological disorders, thereby giving little basis for neuropsychological speculation via this route of making inferences about mechanisms from neurological models.

Most hallucinations take the form of voices talking to or about the patient. Currently, the most successful cognitive accounts of auditory hallucinations propose that these experiences are associated with the patient's own inner speech. Although there are (surprisingly) no large scale systematic surveys, there are many reports of individual cases in which subvocal (whispered) speech was occurring with the same content as the "voice" reported by the patient. Inner speech plays a major role in normal cognition. It is used in verbal short-term memory and in various kinds of problem solving. Indeed, a good case can be made for inner speech as the basis of most thought processes. There is some evidence that the occurrence of some types of hallucinations (e.g., thought echo) do interfere with those cognitive processes that depend upon inner speech.

The abnormality in a hallucinating patient is not the occurrence of inner speech, however, but the patient's experience of it as alien (and possibly its content). Hoffman has suggested that the patient's speech is perceived as alien because it is disorganized. This results in thoughts occurring which are unexpected because they do not fit in with the current plan. Being unexpected, they are perceived as alien.

Others (e.g., Frith) have explained hallucinations in terms of a failure or self-monitoring. Normally we do not have to wait for the consequences of our actions to know what we intended to do or say. We are aware of our intentions before we act. A lack of this special kind of awareness (self-monitoring) would result in speech or thought occurring without intention. Such speech could be perceived as alien. This explanation would also apply to certain delusions, such as thought insertion and delusions of control.

There is some experimental evidence that patients with these kinds of symptoms have difficulty with tasks that require central monitoring of action. Self-monitoring has its physiological counterpart on corollary discharge (or reafference). This is a mechanism by which signals are sent from motor to sensory areas. Such signals enable the sensory consequences of motor actions (such as eye movements or limb movements) to be taken account of. Such mechanisms clearly exist in the human brain, but little is known about them.

Social Interactions

Many features of schizophrenia can be described as abnormalities in the realm of social interactions. Paranoid delusions, for example, result from the patient making incorrect inferences about the intentions of other people or the meaning of stimuli in the surrounding environment. In addition, many of the language disorders shown by some patients arise because of a failure to take account of the needs of the listener if s/he is to understand what the patient is talking about. This ability to infer the beliefs and intentions of other people (sometimes referred to as "mentalizing" or "having a theory of mind") has recently been studied intensively in children. There is evidence that children with autism fail to develop this ability or develop it very slowly. On the basis of autism it has been suggested that there is probably a discrete cognitive module, with an associated discrete brain system that underlies the ability to mentalize. Little is known about this brain system. Since mentalizing is probably a uniquely human ability, studies with animals can only give indirect clues. Brothers has speculated on the physiological basis of "social cognition." She proposes that the amygdala, the superior temporal cortex, and the orbital frontal cortex may be critical components in this system. If some schizophrenic patients do indeed have an "acquired" disability in making inferences about the beliefs and intentions of others, then these seem likely areas to find abnormalities of brain function. New developments in functional brain imaging have the potential to make considerable progress in relating high level cognitive processes to specific brain systems.

Other General Models of Cognitive Dysfunction

Investigators who approach schizophrenia from the general perspective of cognitive neuroscience have become steadily more interested in developing general models that might explain both the generalized cognitive deficits that occur in schizophrenia and the diversity of symptoms. Most of these models emphasize the importance of a basic mental process that is disturbed in patients with schizophrenia and that can be evaluated with the methods of neuroimaging, neurophysiology, and even animal models.

Working Memory (Representationally Guided Behavior)

One of the most popular current models for the cognitive deficit in schizophrenia is that it is due to an inability to guide behavior by representations, often referred to as a defect in working memory. Working memory, or the ability to hold a representation "online" and perform cognitive operations using it, permits individuals to respond in a flexible manner, to formulate and modify plans, and to base behavior on internally-held ideas and thoughts rather than being driven by external stimuli. A defect in this ability can explain a variety of symptoms of schizophrenia. For example, the inability to hold a discourse plan in mind and monitor speech output leads to disorganized speech and thought disorder; the inability to maintain a plan for behavioral activities could lead to negative symptoms such as avolition or alogia; the inability to reference a specific external or internal experience against associative memories (mediated by cortical and subcortical circuitry involving frontal/parietal/temporal regions and the thalamus) could lead to an altered consciousness of sensory experience that would be expressed as delusions or hallucinations. The model also explains the perseverative behavior observed in studies using the Wisconsin Card Sorting Test and is consistent with the compromised blood flow to the prefrontal cortex in these patients.

Sensory Gating Abnormalities

A model that emphasizes the importance of sensory gating and information processing begins from the perspective of techniques used to measure brain electrical activity, particularly various types of evoked potentials, and hypothesizes that the core underlying deficit in schizophrenia involves information processing and attention. This model derives from the empirical clinical observation that patients with schizophrenia frequently complain that they are bombarded with more stimuli than they can interpret. Consequently, they misinterpret (i.e., have delusions), confuse internal with external stimuli (hallucinations), or retreat to safety ("negative symptoms" such as alogia, anhedonia, or avolition). This model has been explored and supported using neurophysiological paradigms to examine sensory gating such as repulse inhibition.

Cognitive Dysmetria

Motor dysmetria has been observed in schizophrenia since its original description by Kraepelin, and "soft signs" of poor coordination are reported in more contemporary studies. More injurious, however, is the related "cognitive dysmetria," which produces "poor coordination" of mental activities. The word "metron" literally means "measure:" a person with schizophrenia has a fundamental deficit in taking measure of time and space, in making inferences about interrelationships between himself and others, or between past, present, and future. He cannot accurately time input and output, and therefore he cannot coordinate the perception, prioritization, retrieval, and expression of experiences and ideas. This hypothesis has received strong support to date from work with PET, which has revealed abnormalities in frontal-thalamic-cerebellar circuitry across a broad range of cognitive tasks.

Some Widely Used Cognitive Tests

Neuropsychological and cognitive functions are frequently assessed with a variety of standard tests that are widely used. Some of these have been carefully normed in order to determine effects of factors such as age and gender and have corrections built in for these factors. Others have not received such careful psychometric assessment, but are widely used because of perceived clinical utility. Some have been validated through study of patients with specific types of brain lesions.

In general, it is best to conceptualize these various tests as useful exploratory tools that have an imputed significance (e.g., tests of executive function, fluency, attention) that is at best provisional. They are divided into categories for purposes of convenience, rather than because they have been definitively shown to assess a particular faculty.

General Tests

WAIS-R: The WAIS-R is perhaps the most widely used method for assessing intellectual function in adults. The revised version has now supplanted the earlier form in most centers. The WAIS-R is, of course, incorporated into some standard assessment batteries, such as the Halstead-Reitan, and so using it permits comparison with data collected in other centers. The WAIS-R is a comprehensive and flexible tool for assessing cognition, since it permits comparison of verbal versus performance function, and examines aspects of attention, perception, motor speed, social judgment, and the ability to think abstractly.

Raven Progressive Matrices: The Raven Matrices were developed as an alternative to standard tests of intellectual function such as the WAIS-R, with the goal of achieving a test that is culture free. The WAIS depends on assessing vocabulary, general information, and other abilities that may be strongly influenced by personal experience and educational background. The Raven Matrices present a series of "pattern puzzles" of increasing complexity, and the subject is asked to identify the final item needed to complete the pattern in a nine-item (three by three) matrix. Regular and advanced sets are available for adults, as well as a version for children. The test has not, however, been well-normed.

Multilingual Aphasia Battery: This test was developed to assess language functions in individuals who might be suffering from aphasia. It contains components that test syntactic and semantic ability, repetition, reading, fluency, and other language functions. In some instances, it may be a useful assessment instrument for patients with schizophrenia, particularly those with disorganized speech.

Mini-Mental Status Exam: This is a very simple screening instrument used to assess mental status in a standardized manner. It covers functions such as orientation, memory, reading ability, and ability to follow a simple command. It provides a summary score that can be used as a quantitative measure of the intactness of mental functions.

Attention

Continuous Performance Task: The CPT is perhaps the most widely used test of attention currently available. The CPT was originally developed to detect deficits in sustained alertness in patients with brain damage. A number of different versions of this task are available, but most involve attentional tasks in which patients observe series of letters or numbers that are presented very briefly one at a time with a relatively short interval in between, and the subject is asked to press a button each time that a predesignated target stimulus appears in a random series.

Trails A and B: These tests are widely used components of the Halstead-Reitan Battery used to assess attention and sequencing. The individual is asked to connect items in a series (i.e., A to 1, B to 2, etc., from among items randomly selected on a page.)

Executive Function

Wisconsin Card Sorting Test: This test is widely regarded as an important test for assessing problem-solving abilities and the capacity to alter response set. The test involves sorting cards according to color, shape, or number. Intermittently, the individual is "corrected" while using a sorting strategy, and at that point must recognize that s/he needs to shift response set.

Stroop Test: This test also assesses capacity to shift response set, as well as attention and mental control.

Porteus Mazes: These are standard maze tests, in which the ability of the subject to plan is challenged by the task of figuring out a path between the entrance and exit of a maze.

Tower of London: This is a planning task, which requires the subject to develop a strategy for moving balls lined up on sticks from an initial position to a final goal position.

Fluency

Many patients suffering from schizophrenia have an impairment in their ability to generate spontaneous ideas or activities. Important clinical correlates are symptoms such as alogia and avolition. Several tests are used to assess fluency, which is also often considered to be a "frontal" function.

Controlled Oral Word Association Test: The COWA assesses the subject's verbal fluency by providing probes, such as asking the subject to name as many words as possible that start with the letter D. This test has been widely used as part of the Multilingual Aphasia Examination.

Category Fluency Test: This task assesses the subject's fluency by asking them to name as many words as possible that belong to a specific semantic category (e.g., "animals," "fruits," "vegetables"). One minute is allowed for each category.

Verbal Memory

Verbal memory is an important temporolimbic function, and therefore it may be important to assess its dimensions in patients suffering from schizophrenia.

Logical Memory (Wechsler Memory Scale): This memory task involves having the subject listen to a coherent story and then recall as many details of the story as possible. Both immediate and delayed recall are assessed.

Rey Auditory Verbal Learning Test: This test involves determining the subject's capacity to learn a list of words by rote. Both immediate memory and delayed recall are assessed. A learning curve is also established.

Paired Associate Learning: This somewhat more complicated memory task asks for a subject to learn a list of words that are associated with a cue set of words (e.g., metal-iron, baby-cries).

Visual Reconstructive Memory

Although most of the theoretical literature and data-based research implicates left hemisphere abnormality in schizophrenia, it is important to study right hemisphere function as well. The following tests of visual reconstructive memory are frequently considered to assess right hemisphere function.

Rey-Osterreith Complex Figure: This task involves showing a complex figure to the subject, having him copy it, and having him draw it again from memory immediately and after a delay. Although this task is somewhat difficult to administer, it can be given in a reliable and standardized way to do so by giving the subject colored pencils in a set sequence of time.

Benton Visual Retention Test: This widely used test examines the ability to copy and recall a variety of figures and shapes.

Motor Function

It may be important to assess motor function in patients with schizophrenia, both because motor slowness may be a correlate of negative symptoms, and because of the motor side-effects of neuroleptic medication.

The Finger Oscillation Test: This test measures tapping speed with the left and right hands. It gives a measure of overall motor speed as well as an assessment of lateral asymmetries in motor performance.

Purdue Pegboard: This test was developed to assess manual dexterity. Fine motor performance is assessed with the right hand, the left hand, and then both hands simultaneously. It provides a useful measure of lateralization.

6. NEUROPHYSIOLOGY

In the process of encoding, processing, and transferring information, the human brain generates an ongoing array of electrical signals. In fact, important electrical activity also occurs during periods of apparent rest, as during sleep, and while individuals are dreaming. Investigators interested in studying and understanding the human brain have recognized for decades that they can potentially evaluate it noninvasively by developing methods for measuring this electrical activity by making recordings from the brain surface. These methods are embodied in neurophysiology.

Neurophysiological techniques have many advantages for the study of the human brain and its abnormalities. They are noninvasive, and therefore usually quite acceptable to severely disturbed patients. They require only a minimum quantity of technical equipment, and therefore can be used in sites that do not have access to high-technology methods for research such as MR or PET. Further, they examine brain activity during very short time windows (i.e., milliseconds) and therefore are potentially able to capture mental states that are extremely brief. The signal obtained from these techniques is often weak, however, and therefore many of the neurophysiological methods depend on repeated measurements and signal averaging to summarize the information obtained and extract the signal from its background noise. An additional problem with neurophysiological techniques is that they are especially sensitive to a variety of artifacts and confounders, including subject movement, the effects of medications, and the influence of electrical signals and other "noise" in the surrounding environment. Several different kinds of methods have been applied.

Neurophysiological techniques include electroencephalography (EEG), Brain Electrical Activity Mapping (BEAM), Event Related Potentials (ERP), and measurement of Smooth Pursuit Eye Movements (SPEM). All of these methods have been applied to the study of schizophrenia, with variable levels of success.

Electroencephalography (EEG)

EEG is the oldest of these techniques, having been discovered by the psychiatrist Hans Berger in 1929. Since that time standardized methods have developed for the recording of brain electrical activity. These involve a standard format for the placement of electrodes, referred to as the International 10-20

System. Clinical EEG places these electrodes in frontal, temporal, parietal, occipital, and central positions (proportionally correcting for head size) and uses both ears as reference electrodes. The activity measured is conventionally broken down into four frequency bands: beta (>12 Hz), alpha (8-12 Hz), theta (4-7 Hz), and delta (<4 Hz). Patterns of activity vary in the normal brain according to region and mental state. Beta activity is typically seen frontally, while alpha is usually occipital. Theta activity emerges when an individual is drowsy, while delta activity occurs during sleep. Some drugs (e.g., benzodiazepines) enhance beta activity, while others (e.g., lithium) induce theta activity. In normal waking individuals, delta activity (especially focal delta) is not seen; its presence typically suggests some type of abnormality or injury, such as a tumor or subdural hematoma.

No specific EEG abnormalities have been observed in schizophrenia, although the technique has been applied in many studies. The principal use of EEG in the study of schizophrenia is clinical. In cases with an unusual presentation, it may be used to evaluate the possibility of some type of neurological or medical condition.

Brain Electrical Activity Mapping (BEAM)

BEAM is a more recent development from the basic technology of EEG. BEAM takes advantage of the efficiency and memory of computers and provides a method for collecting and storing larger amounts of information than can be routinely collected during a clinical EEG. The data are then subjected to a Fast Fourier Transformation (a common tool in neuroimaging) and displayed as a color map. This visually appealing presentation resembles that provided through the neuroimaging techniques described earlier. However, the picture created may portray a map of brain electrical activity from a single individual displayed as a "difference map," which compares that specific individual to a set of norms that have been collected from a group of individuals. In the early days of BEAM, it was hoped that this might provide a diagnostic tool that would depict clear differences between an individual with a specific illness such as schizophrenia or mania and the normative group. This promise has not, however, been fulfilled. Early reports of "hypofrontality" in schizophrenia that employed BEAM are now recognized to be based on the fact that more eye movement artifacts occurred in the schizophrenic patients. (The eye is a large dipole, and during movement it produces enormous slow waves which mimic delta activity.)

Although BEAM may have some applications in research on the pathophysiological mechanisms of schizophrenia, the above example indicates that it must be used with great care. It does not have any clearcut clinical applications that add anything to the information provided by simpler EEG methods.

Event Related Potentials (ERPs)

ERP techniques have been considerably more productive in the search for mechanisms of brain abnormality in schizophrenia. Event-related potentials involve the study of electrical activity in relationship to some type of stimulus, typically one that involves information processing. An ERP may be negative or positive. It is designated in relationship to its position in relation to the stimulus and its positivity or negativity. Three common ERPs that have been studied by neurophysiologists are the N100 (a negative wave occurring at 100 milliseconds), the P50 (a positive wave occurring at 50 milliseconds), and the P300 (a positive wave occurring at 300 milliseconds). These potentials are usually observed and measured through the administration of repeated stimuli to produce an averaged response, which enhances the signal to noise ratio. These (and a variety of other types of ERPs which have also been studied) are thought to be related to different specific aspects of information processing. The region in the brain thought to be responsible for producing or modulating them is referred to as the "generator."

N100

The N100 is thought to be related to selective attention, as opposed to unattended stimuli. It has been studied through information processing paradigms that require the subject to focus attention, such as those involving dichotic listening (giving competing and different stimuli to the two ears), sometimes with attentional instructions (attend to the right or left ear). Changing the instructions affects the appearance of the waveform. This ERP has not been extensively studied in patients with schizophrenia, but studies using the dichotic listening paradigm with PET neuroimaging have demonstrated abnormalities in attentional circuitry.

P300

The P300, on the other hand, has been the subject of numerous investigations. This wave is increased when the subject is given new information to process or an unexpected type of stimulus.

Patients with schizophrenia have been shown to have a decreased P300. The decrease in the P300 has been shown to be correlated with a decrease in temporal lobe size, suggesting that this region may be its generator. Patients show a differential improvement in P300 response in relation to clinical improvement depending on whether the stimulus is provided visually or auditorily. The improvement correlates primarily with visual response rather than auditory response. The abnormalities in the P300 are thought to reflect either a decrease in overall attentional resources or in the ability to allocate them.

P50

The P50 has also been useful in the study of "sensory gating" in schizophrenia. Sensory gating refers to the ability to filter stimuli and to differentiate important or relevant stimuli from those that are unimportant or irrelevant. It has been studied with several different paradigms. One involves "prepulse inhibition," or the delivery of a weak novel signal prior to delivery of a strong novel signal that would normally induce a strong startle response (e.g., an unexpected loud noise). In normal individuals the P50 is reduced by prepulse inhibition, but it is not reduced in schizophrenic patients, suggesting that they have a basic deficiency in their ability to filter information; operationally, this suggests that patients with schizophrenia experience an internal atmosphere where they feel continually bombarded with stimuli to which they are unable to adapt. A second paradigm that has also been used to study the P50 involves a "sensory gating" paradigm. This paradigm is similar to prepulse inhibition, in that it involves two paired stimuli, the first of which serves to dampen the response to the second. In this case the paradigm involves measuring the P50 when two auditory click stimuli are given 500 milliseconds apart. In normals the P50 is greater in response to the first click than the second, while patients with schizophrenia are unable to attenuate the response to the second click. By inference, they are in a continual state of arousal and are unable to filter, prioritize, or gate. As for the P300, the P50 abnormality may be linked to the temporal lobe. It has also been observed in patients with schizotypal disorder and may also be present in first-degree relatives of patients with schizophrenia.

Smooth Pursuit Eye Movements (SPEM)

Disorders in the ability of schizophrenic patients to track a moving target were noted initially by Holzman in the 1970s and were thought to be related to an abnormality in attention. This work has been consistently replicated since the early reports and has been relatively robust to a search for possible confounders, such as effects of medication or task performance. The abnormality involves a loss of smoothness in the tracking pattern, which is marked by saccadic intrusions. It can be measured either by a visual rating system, by quantifying pursuit gain (a measure of eye movement velocity in relation to target velocity), or by counting the number of saccadic intrusions. In many cases, the number of saccadic intrusions is increased in schizophrenia even when pursuit gain is normal. The saccadic intrusions probably represent "catch up" movements to attempt to make up for inability to match target velocity.

The study of SPEM has been linked in many studies to evaluation of first degree relatives of schizophrenic patients, who have an increased rate of SPEM abnormalities as compared to controls or relatives of patients with affective disorders. These findings are consistent with the possibility that SPEM abnormalities are a trait or vulnerability marker for schizophrenia. Studies of SPEM are now being coupled with linkage studies in an effort to identify the gene(s) that may be involved in the abnormality.

7. NONGENETIC FACTORS

When Emil Kraepelin presented his concept of dementia praecox almost 100 years ago, he was convinced that the illness was due to a degenerative illness of the brain. Empirical evidence did not appear until 60 years later, however, when it was shown through pneumoencephalography that patients with schizophrenia had enlarged cerebral ventricles. As described in the genetics section of this module, twin and adoption studies have provided compelling evidence for the importance of both genetic transmission and environmental stressors as possible etiologic factors for schizophrenia. At present, it is not clear how much the multiple structural and functional brain abnormalities that have now been widely documented through neuroimaging techniques are the result of genetic or environmental factors, although it appears likely that both play a role and that the distinction between genes versus environment is to some extent a false dichotomy.

Prospective longitudinal studies of people at risk for schizophrenia can be a powerful method in order to disentangle genetic and environmental influences. This strategy permits investigators to ascertain why some individuals at risk become ill while others do not. The first study of this kind in

psychiatry was initiated in Copenhagen in 1962. A sample of 207 children of schizophrenic mothers and 104 matched low risk controls were studied and assessed from 1962-64. Eventually they were followed up and reassessed in 1965-67, 1972-74, and 1986-89. At the first assessment they were all between 10-20 years of age (average 15 years). The results of this study have provided useful information that has illuminated the roles of both environmental and genetic factors in schizophrenia. The results summarized here illustrate the importance of these influences, and particularly the potential role of birth injuries and viral infections.

Obstetrical Complications

A number of hypotheses can be explored in studies of this type. One is that those who would eventually become ill with schizophrenia might have been exposed to some kind of brain damage before the illness became manifest. Prenatal injury or obstetrical complications are possible causes of such brain damage. Intrauterine bleeding could damage the neural development of the fetus. Obstetrical complications which cause hypoxia or induce regional injury (e.g., use of forceps causing regional hemorrhage, neural tissue compression due to intense contractions or a narrow birth canal) are more common. Some of the well known cognitive dysfunctions observed in children such as dyslexia are thought to be at least partially due to obstetrical complications.

In the 1962 Copenhagen High Risk Study, compulsory midwife reports were used to determine the frequency of such complications. These reports contain information about the course of pregnancy (major complications such as bleeding, pre-eclampsia, and eclampsia), the course of the delivery, and the status of the newborn child. After the subjects in this cohort were identified, the investigators waited until the subjects had reached the age of risk for schizophrenia. At this time, they could then begin to determine whether there was a positive correlation between obstetric complications and incidents of schizophrenia. When the first report on this topic was published based on the follow-up in 1972-74, approximately half of the patients expected to develop schizophrenia had become manifest. Those who developed schizophrenia indeed had a higher rate of obstetric complications. In contrast, however, high-risk individuals diagnosed as having schizotypal personality disorder had very few complications, even fewer than the normal controls. These results were interpreted within the context of the Danish American adoption studies, which found that schizophrenia and schizotypal disorder were both prevalent in full siblings, who shared the same schizophrenic biological parent. Taken together, the two sets of findings led to the hypothesis that schizophrenia might be a neurologically complicated form of schizotypal personality disorder, which could be considered as a more direct representation of the schizophrenic genotype than was schizophrenia itself.

In order to test this hypothesis, a subsample of the high-risk sample was evaluated with a repeated diagnostic research interview and CT scanning. The sample consisted of schizophrenics, schizotypals, and mentally healthy high-risk subjects. The patients with schizophrenia had the largest cerebral ventricles, while those with schizotypal disorder had the smallest. The ventricular size of the healthy offspring of schizophrenic mothers was in between. Furthermore, a significantly positive but not modest correlation was found between ventricular size and the level of perinatal complications.

In the 1986-89 follow-up of the total sample, CT scanning was repeated on a much larger scale. The earlier results were repeated, in that the schizotypal subjects showed a ventricular size similar to the healthy high-risk subjects, whereas the subjects with schizophrenia had more ventricular enlargement and more sulcal prominence. This follow-up study also demonstrates that the ventricular enlargement in the high-risk group was a result of an interaction between the level of genetic risk and the severity of the pregnancy and birth complication score. When obstetrical complications were controlled for, the children of schizophrenic mothers had larger cerebral ventricles than had the low-risk control children. If the children of a schizophrenic mother also had a father within the schizophrenia spectrum, the ventricular enlargement was even larger.

Pregnancy and birth complications seem to be a well-established contributing factor in the pathogenesis of schizophrenia. In principle, this knowledge can be used for primary preventive intervention, through the use of close follow-up and early treatment interventions in high-risk samples. However, there are potential ethical problems associated with a preventive strategy of this type. First, it may have a negative influence on the prospective mother's expectations, if she knows that she receives special pregnancy care because she has a first-degree relative who suffers from schizophrenia. Second, there is also a risk of producing a "self-fulfilling prophesy" in the high-risk child or adolescent, who may have increased anxiety or lowered self esteem because of an "at-risk" status. These ethical problems have to be weighed against possible benefits.

Viral Infections

Multiple studies have shown a relationship between season of birth and the development of schizophrenia. In the northern hemisphere more individuals who develop schizophrenia are born in the first 4 months of the year, whereas the pattern is reversed in the southern hemisphere (July through September). The seasonal variation is most pronounced in larger industrialized areas in the northwestern part of the northern hemisphere, as well as in urban regions as compared with rural regions. The precise factors accounting for these findings are still a matter of debate. Industrialized megacities are characterized by large low-income areas and large population density. This combination could result in an increasing risk of developing influenza, and as well the negative influences of poverty and its associated social and educational deprivation. Either of these factors, as well as an interaction between them, might predispose to the development of schizophrenia.

The first empirical study suggesting the role of influenza was published in 1988. This study reported on a pandemic of A2-influenza that occurred in Helsinki, Finland, in November 1957. The rate of influenza was measured among children who were born in Helsinki to mothers who were in the second trimester of pregnancy during the peak period of the pandemic. When the rate of schizophrenia during this time period was compared to the rate among children born at the same time of the year during the preceding five years without influenza epidemics, the rate of schizophrenia was 80% higher among the cohort exposed to influenza. Since that time, several studies have successfully replicated the findings from the original Helsinki investigation, including reports originating in England and Wales, Scotland, Ireland, Japan, and Australia. Inevitably, there have also been some failures to replicate.

Despite the methodologic pitfalls in this type of study, the convergence of results suggest that exposure to the influenza virus could be one contributing factor to the pathogenesis of schizophrenia. The results of these studies have important epidemiologic significance, since influenza is a pathogenic factor that can be prevented through vaccination. There is no evidence suggesting a risk to the fetus in connection with vaccination of pregnant women against influenza. Therefore, vaccination during the first half of pregnancy should be considered as a possible preventive measure.

Nutritional Factors

In addition to obstetrical complications and viral infections, several other non-genetic factors appear to be associated with a higher rate of schizophrenia. The role of poorer nutrition has been studied through investigating the incidence of schizophrenia in the children of mothers whose pregnancy occurred during the "Dutch hunger winter" at the end of the Second World War, a time when food supplies were extremely scarce. Children born to these mothers have a substantially increased risk for schizophrenia in comparison with the general population. These results suggest that a variety of nongenetic influences can contribute to the development of schizophrenia.

General Conclusions

During the past several decades a consensus has gradually emerged concerning the etiology and pathophysiology of schizophrenia. Most investigators consider it to be a neurodevelopmental disorder. Within that general framework, however, some controversy remains concerning the role of genetic versus non-genetic factors and the timing of the developmental insult. Early theories stress the importance of prenatal and perinatal complications (e.g., birth injuries, viral infections), superimposed upon a genetic diathesis. More recently, as more has been learned about the evolution of brain development in childhood and adolescence, others have suggested that schizophrenia should at least in part be conceptualized as a "late neurodevelopmental disorder." Studies of normal brain development have demonstrated that normal brain maturation is a process that continues into the early 20s. Normal brain growth is characterized by an early proliferation of neuropil followed by a process that prunes this overgrowth during adolescence and young adulthood (leading to a measurable decrease in grey matter volume during this time period). One much-discussed theory concerning the pathogenesis of schizophrenia is that an aberration occurs in this normal process, perhaps due to problems in its genetic regulation, leading to the general reduction in brain size that has been frequently reported in MR studies of schizophrenia.

As described in Module 1, the question of whether schizophrenia should be conceptualized as a single disease entity or multiple diseases remains an open question. In part, however, the answer to the question depends on the "level" that one is discussing. At the level of the phenotype (i.e., clinical symptoms), schizophrenia is clearly diverse. At the level of etiology, it is probably diverse as well. That

is, it appears highly unlikely that the cause of schizophrenia could be limited to a single gene or even to multiple genes acting independently of non-genetic influences. Rather, investigators are beginning to think of schizophrenia much as we think about cancer. That is, cancer is a single illness in that it is defined by a single pathophysiological mechanism – abnormal cell proliferation. In the case of cancer, the phenotype is heterogeneous, in that the cell proliferation may occur in many different organs such as the lungs or the brain. Likewise, cancer can be induced through purely environmental influences if they are extremely severe (radiation exposure, perhaps within the context of a depressed immune system), but it can also be heavily or predominantly genetic. Andreasen has suggested that we should think of schizophrenia in a similar way, using a “working model” that posits multiple etiologies ranging from genetic to non-genetic (i.e., regulation of gene expression, nutrition, viral infections, birth injuries, etc.), which usually must accumulate to induce a “multiple hit effect,” which in turn leads to the development of schizophrenia if sufficient “hits” accumulate. Despite the diversity of etiology, however, the multiple factors converge on a single pathophysiology, abnormalities in brain development that lead to a “misconnection syndrome,” which leads in turn to a fundamental cognitive abnormality that was originally described by Bleuler as “loosening of associations.” In the 21st century, we now conceptualize Bleuler’s “loosening of associations” as impaired information processing, disturbed monitoring of thoughts, or poor mental coordination. This fundamental impairment in cognition leads in turn to generalized impairment in multiple mental processes, including attention, memory, language, and emotion. These multiple cognitive impairments lead in turn to the diversity of symptoms, as manifested in the diverse phenotype. A model such as this is Heuristic, in that it permits investigators to focus on the factors that regulate neurodevelopment and the formation of neural circuits and neural communication. A relatively simple model of this type is useful, since it suggests promising areas of research that may lead ultimately to improvements in treatment or preventive measures, since it suggests the importance of examining neurodevelopment as a primary target.

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