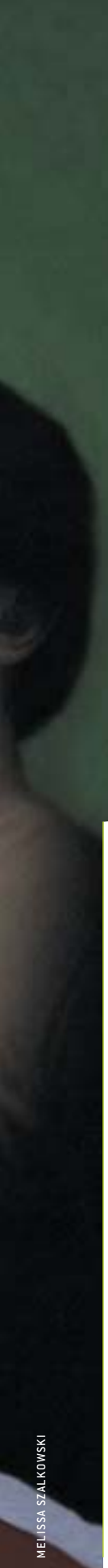
DIAGNOSING DISORDERS

PSYCHIATRIC ILLNESSES ARE OFTEN HARD TO RECOGNIZE, BUT GENETIC TESTING AND NEUROIMAGING COULD SOMEDAY BE USED TO IMPROVE DETECTION

BY STEVEN E. HYMAN



MELISSA SZALKOWSKI

Brain disorders usually have behavioral symptoms that can be observed by a psychiatrist. But the checklist approach to diagnosis is far from perfect.

ACCURATE DIAGNOSIS IS THE CORNERSTONE OF medical care. To plan a successful treatment for a patient, a doctor must first determine the nature of the illness. In most branches of medicine, physicians can base their diagnoses on objective tests: a doctor can examine x-rays to see if a bone is broken, for example, or extract tissue samples to search for cancer cells. But for some common and serious psychiatric disorders, diagnoses are still based entirely on the patient's own report of symptoms and the doctor's observations of the patient's behavior. The human brain is so enormously complex that medical researchers have not yet been able to devise definitive tests to diagnose illnesses such as schizophrenia, autism, bipolar disorder or major depression.

Because psychiatrists must employ subjective evaluations, they face the challenge of reliability: how to ensure that two different doctors arrive at the same diagnosis for the same patient. To address this concern, the American Psychiatric Association in 1980 published the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (widely known by the acronym "DSM-III"). Unlike earlier editions of the manual, DSM-III and its successor volumes (the latest one is referred to as DSM-IV-TR) describe what symptoms must be present—and for how long—to make a diagnosis of a particular brain disorder. Virtually all these criteria, however, are based on the patient's history and the clinical encounter. Without the ability to apply objective tests, physicians may fail to detect disorders and sometimes mistake the symptoms of one illness for another's. Making the task more difficult is the fact that some psychiatric illnesses, such as schizophrenia, may turn out to be clusters of diseases that have similar symptoms but require different treatments.

In recent years, though, advances in genetics, brain imaging and basic neuroscience have promised to change the way that brain disorders are diagnosed. By correlating variations in DNA with disease risks, researchers may someday be able to determine which small differences in a patient's genetic sequence can make that person more vulnerable to schizophrenia, autism or other illnesses. And rapid developments in neuroimaging—the noninvasive observation of a liv-

ing brain—may eventually enable doctors to spot structural features or patterns of brain activity that are characteristic of certain disorders. Better diagnosis will lead to better care: after pinpointing a patient's brain disorder, a physician will be able to prescribe the treatment that is best suited to it. And earlier diagnosis could allow doctors to slow or halt the progress of a disorder before it becomes debilitating.

History of Diagnosis

THE FIRST MODERN ATTEMPT to identify individual psychiatric disorders was made in the 19th century by German scientist Emil Kraepelin, who distinguished two of the most severe mental illnesses: schizophrenia, which he called dementia praecox, and manic-depressive illness, which is now known as bipolar disorder. Much of his careful observational work focused on following the course of the illnesses over the lifetime of his patients. He defined schizophrenia as a disease with psychotic symptoms (such as hallucinations and delusions) that had an insidious onset—in other words, the initial symptoms may be hard to detect—and a chronic, downhill course. In contrast, manic-depressive illness was characterized by discrete episodes of illness alternating with periods of relatively healthy mental function.

Some PSYCHIATRIC ILLNESSES may turn out to be clusters of diseases that have similar symptoms but REQUIRE DIFFERENT TREATMENTS.

In the early 20th century, however, work on psychiatric diagnosis went into eclipse as a result of the influence of the psychoanalytic theories developed by Sigmund Freud and his followers. In their conception of mental illness, symptoms arose from a failure to successfully negotiate stages in psychological development. The symptoms of each illness indicated the point in development at which the trouble arose. The psychoanalytic theory of that period did not allow for the possibility that different psychiatric illnesses might have completely different causes, let alone the modern idea that mental disorders might arise from abnormalities in brain circuits.

Diagnosis returned to a central position in psychiatry in the 1950s, though, with the discovery of drugs for treating psychiatric disorders. Researchers found that chlorpromazine (better known by one of its brand names, Thorazine) could control the psychotic symptoms of schizophrenia and that lithium salts could stabilize the moods of patients with bipolar disorder. By 1960 the first antidepressant and antianxiety drugs were introduced. It quickly became critically important to match the patient with the right treatment. The new antidepressants did not work for schizophrenia and could precipitate an episode of mania in someone with bipolar disorder. Lithium was remarkably effective for bipolar disorder but not for schizophrenia.

In the 1980s the publication of DSM-III and subsequent manuals enabled psychiatrists to use standardized interviews and checklists of symptoms to make their diagnoses. Although the checklist approach is imperfect, it represented an enormous advance in both clinical care and research. For example, before the advent of DSM-III, it appeared that schizophrenia was twice as prevalent in the U.S. as it was in Great Britain. This discrepancy turned out to be an artifact of divergent approaches to diagnosis. In fact, the prevalence of schizophrenia is about 1 percent of people worldwide. The standardization of diagnosis made it clear that mental disorders are common and quite often disabling. According to the World Health Organization's data on the global burden of disease, major depression is the leading cause of disability in the U.S. and other economically advanced nations. In aggregate, mental disorders rank second only to cardiovascular diseases in terms of their economic and social costs in those countries.

Meanwhile advances in neuroscience showed that certain neurological diseases leave unmistakable signatures on the brain. Parkinson's disease,

OVERVIEW/*Improving Diagnosis*

- Because psychiatrists lack objective tests for detecting brain disorders, they sometimes fail to observe mental illness or mistake the symptoms of one disorder for another's.
- Scientists have recently found gene variants that seem to confer susceptibility to disorders such as schizophrenia and autism. Doctors may someday be able to determine a patient's risk of developing these diseases by analyzing his or her DNA.
- In addition, advances in neuroimaging may allow physicians to look for subtle anomalies in the brain caused by mental disorders. As the technology improves, doctors could use neuroimaging to diagnose psychiatric illnesses and to track the success of therapy.

for instance, is characterized by the death of nerve cells in the midbrain that make the neurotransmitter dopamine, a chemical that transmits signals between neurons. The definitive signs of Alzheimer's disease are deposits of an abnormal protein called amyloid and tangles of protein in the cells of the cerebral cortex, the outermost layer of the brain. (Because one needs a microscope to observe these anomalies, a conclusive diagnosis can be made only after the patient's death.) But when it comes to psychiatric illnesses such as schizophrenia and depression, the abnormalities in the brain are much more subtle and difficult to discover. For this reason, many researchers have begun to look for indicators of brain disorders in the human genome.

The Genetics of Disorder

JUST AS NORMAL behavioral traits are often passed from parent to child, certain mental disorders run in families. To determine whether the resemblance is a result of genes or family environment, researchers have conducted studies comparing the risk of illness in identical twins (who share 100 percent of their DNA) to the risk in fraternal twins (who on average share 50 percent of their DNA). Another type of study, which is more cumbersome, focuses on whether an illness in offspring who were adopted early in life is more often shared with their biological relatives or their adoptive families.

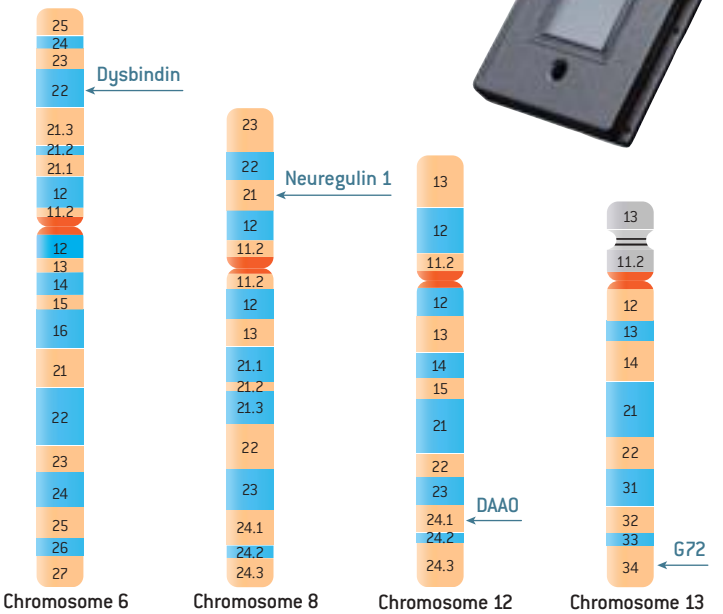
Such studies reveal that genes play a substantial role in the transmission of mental disorders but that other factors must also be at work. For example, if one identical twin has schizophrenia, the risk to the other is 45 percent. If one identical twin has autism—a developmental brain disorder characterized by impairments in communication and social interaction—the other twin has a 60 percent chance of sharing the same diagnosis. These are enormous increases over the risks for the general population (1 percent for schizophrenia, 0.2 percent for autism), but the key point here is that some twins do not develop the disorders even if they carry the same genes as their affected siblings.

Therefore, nongenetic factors must also contribute to the risk of illness. These factors may include environmental influences (such as infections or injuries to the brain early in life) and the random twists and turns of brain development. Even among identical twins growing up in exactly the same environment, it is not possible to wire up a brain with 100 trillion synapses in identical fashion. For all mental disorders—and, indeed, for all normal patterns of behavior that have been studied—genes are important, but they are not equivalent to fate. Our brains, not our genes, directly regulate our behavior, and our brains are the products of genes, environment and chance operating over a lifetime.

What is more, new research indicates that the strong genetic influence on the risk of developing a disorder such as schizophrenia is not the work of a single gene. Rather, the increase in risk seems to be an aggregate effect of many genes interacting with one another and with nongenetic factors. By studying the DNA sequences of people with schizophre-

FIRST STEPS TOWARD A GENETIC TEST?

PEOPLE WHO POSSESS DNA SEQUENCE VARIATIONS in any of the four genes shown below appear to have a slightly increased risk of developing schizophrenia. These genes are involved in the transmission of signals among neurons in the brain, so it is possible that the genetic variations disrupt that process. But possessing the variations is neither necessary nor sufficient to cause schizophrenia, which most likely arises by several pathways. In the future, as researchers learn more about the genetic and nongenetic causes of brain disorders, doctors may be able to estimate a patient's risk of acquiring a psychiatric illness by analyzing his or her DNA with a gene chip (*at right*).



GENE CHIP IMAGE COURTESY OF AFFYMETRIX; SOURCE FOR CHART: NATIONAL ACADEMY OF SCIENCES

THE AUTHOR

From an early age, *STEVEN E. HYMAN* was curious about how our brains underlie thinking, emotion and behavioral control. He studied philosophy as an undergraduate at Yale University and philosophy of science at the University of Cambridge, where he was a Mellon Fellow. After earning his M.D. at Harvard University, he received clinical training in psychiatry and scientific training in molecular neurobiology. He was the founding director of Harvard's Interfaculty Initiative in Mind, Brain and Behavior. From 1996 to 2001 he served as Director of the National Institute of Mental Health, the component of the National Institutes of Health charged with generating the knowledge needed to understand, treat and prevent mental illness. Since 2001 he has been Harvard's provost and a professor of neurobiology at Harvard Medical School.

nia and their family members, researchers have already found several genetic variations that appear to increase susceptibility to the disorder [*see illustration on preceding page*]. These variations occur in genes that code proteins involved in the transmission of signals among neurons in the brain, so it is possible that the variations disrupt that process. Similar studies have identified genetic variations that appear to increase the risk of developing major depression and bipolar disorder. Furthermore, a variation of *HOXA1*, a gene related to early brain development, seems to boost susceptibility to autism. The variant gene is present in about 20 percent of the general population but in about 40 percent of people with autism.

Although possessing the variation of *HOXA1* approximately doubles the risk of developing autism, more than 99.5 percent of people who have the variant gene do not acquire the disorder, and about 60 percent of people with autism do not possess the variant gene. As is the case for many diseases, there is not likely to be a single set of genes that are necessary and sufficient to cause either schizophrenia or autism. Instead these illnesses may arise by several pathways. This situation, called genetic complexity, seems to apply to bipolar disorder and depression as well. Each of these disorders may actually represent a group of closely related mental illnesses that share key aspects of abnormal physiology and symptoms but may differ in details large and small, including severity and responsiveness to treatment.

Genes are not equivalent to fate. Our brains are the PRODUCTS OF GENES, ENVIRONMENT AND CHANCE operating over a lifetime.

What are the implications for diagnosis? Imagine that variations in 10 distinct genes can boost the risk of developing a mental illness but that none of the genetic variations by itself is either necessary or sufficient to bring on the disorder (this is close to a current model for autism). Different combinations of the variant genes may confer risks of similar but not identical forms of the illness. To correlate all the possible genetic combinations with all the clinical outcomes would be an immensely complex task. But the tools for such an undertaking are already available. Thanks to technologies developed for the Human Genome Project, scientists can rapidly determine what variations are present in a person's DNA. Using gene chips—small glass slides holding arrays of thousands of reference DNA samples—researchers can also discover which genes are actively coding proteins in a given cell or tissue.

If the gene-hunting effort is successful, doctors will someday be able to analyze a patient's genetic sequence and see where it fits in the matrix of risks. The accuracy of this matrix would be greatly enhanced if physicians also had more information about environmental risk factors. In all likelihood, none of the environmental influences has an overwhelming effect on illness risk—otherwise, researchers would have probably noticed it by now—so epidemiologists will need to study large numbers of people to tease out all the small contributions. By taking both genetic and environmental factors into account, this method may be able to determine whether a person is at high risk for acquiring a particular brain disorder. High-risk patients could then receive close scrutiny in follow-up observations, and if symptoms of the disorder appear, doctors would be able to begin treatment at the earliest stages of the illness.

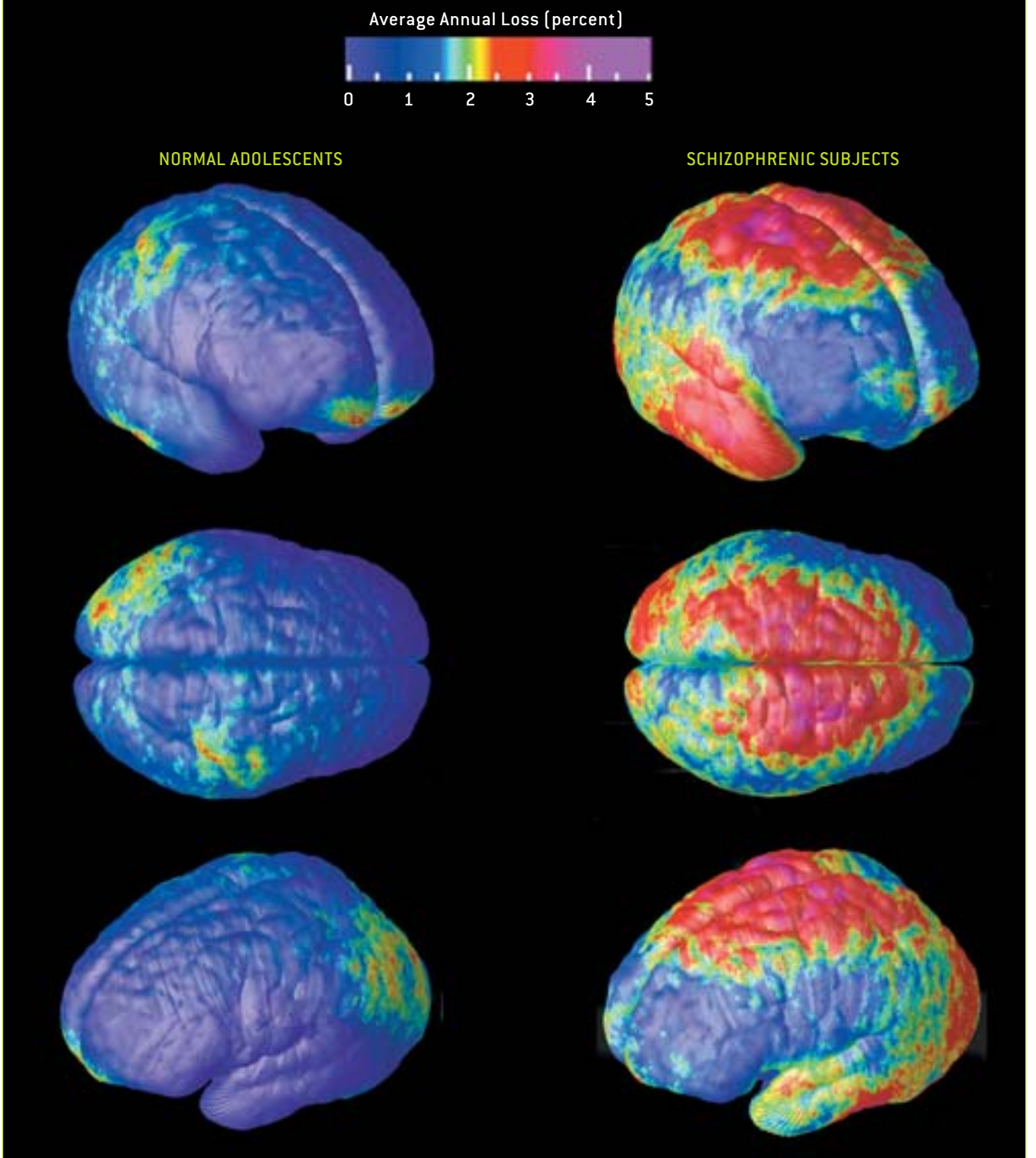
For patients already showing symptoms of a disorder, their genetic information would be quite useful in narrowing down the diagnostic possibilities. And as researchers learn how genetic variations can affect responses to drugs, knowing a patient's genomic profile could help a physician choose the best treatment. But there is a downside to this medical advance: in a society where people can carry their DNA sequences on a memory chip, policymakers would have to grapple with the question of who should have access to this data. Even though a genetic sequence by itself cannot definitively predict whether a person will descend into depression or psychosis, one can readily imagine how employers, educational institutions and insurance companies might use or misuse this information. Society at large will have to become far more sophisticated in its interpretation of the genetic code.

Imaging the Brain

MOVING IN PARALLEL with the genomic revolution, neuroscientists have dramatically improved their ability to image the living brain noninvasively. There are three major types of neuroimaging studies. The first is morphometric analysis, which

TELLTALE SIGNS IN THE BRAIN

THREE-DIMENSIONAL MAPS of the brain derived from magnetic resonance imaging reveal that one type of schizophrenia causes a characteristic pattern of tissue loss in the cerebral cortex. The maps show that the average annual reduction in the cortical gray matter of adolescent patients suffering from childhood-onset schizophrenia (*right*) is much greater than the loss in healthy teenagers (*left*) between the ages of 13 and 18.



COURTESY OF PAUL THOMPSON AND ARTHUR W. TOGA *UCLA Laboratory of Neuro Imaging* AND JUDITH L. RAPOPORT *National Institute of Mental Health*

THE SPECTRUM OF PSYCHIATRIC ILLNESS

MENTAL DISORDERS, which afflict millions of people every year, can be hard to diagnose. As the table shows, some illnesses have overlapping symptoms. Certain mood disorders, such as major depression and dysthymia, have similar symptoms but differ in severity. Among anxiety disorders, the primary distinction is the trigger that initiates fear, panic or avoidance behavior. Psychotic disorders also range from mild to severe. More definitive diagnostic methods are clearly needed.

DISORDER	COMMON SYMPTOMS	PREVALENCE (PERCENT)*
MOOD DISORDERS		
Major Depression	Characterized by episodes during which the patient feels sad or empty nearly every day; loses interest or pleasure in hobbies and activities; experiences changes in appetite, weight, energy levels or sleeping patterns; or harbors thoughts of death or suicide	5.3
Dysthymia	Similar to major depression, but the symptoms are less severe and more chronic. Sad or empty mood on most days for at least two years. Other symptoms include low self-esteem, fatigue and poor concentration.	1.6
Bipolar I	Episodes of abnormally elevated or irritable mood during which the patient feels inflated self-esteem; needs less sleep; talks more than usual; or engages excessively in pleasurable but unwise activities. These manic periods may alternate with depressive episodes	1.1
Bipolar II	Depressive episodes alternate with less severe manic periods that do not markedly impair functioning or require hospitalization	0.6
ANXIETY DISORDERS		
Specific Phobia	Excessive or unreasonable fear of a specific object or situation, such as flying, heights, animals, receiving an injection or seeing blood. Exposure to the stimulus may provoke a panic attack (palpitations, sweating, trembling, shortness of breath, etc.)	8.3
Agoraphobia	Anxiety about being in any place or situation from which escape might be difficult. Typical fears involve being alone outside the home, standing in a crowd, crossing a bridge, or traveling in a bus, train or automobile	4.9
Post-traumatic Stress Disorder	Patient persistently reexperiences a traumatic event through distressing recollections, recurring dreams or intense reactions to anything symbolizing or resembling the event	3.6
PSYCHOTIC DISORDERS		
Schizophrenia	Characterized by delusions, hallucinations, disorganized speech, inappropriate or blunted emotional responses, loss of motivation and cognitive deficits	1.3
Schizophreniform Disorder	Similar to schizophrenia, but the symptoms last for less than six months and may not be severe enough to impair social or occupational functioning	0.1

**Percent of U.S. population between ages 18 and 54 suffering from the disorder in any one-year period.*

SOURCES: NATIONAL INSTITUTE OF MENTAL HEALTH; *DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS*, FOURTH EDITION, 1994

generally relies on high-resolution magnetic resonance imaging (MRI) to produce precise measurements of brain structures. The second is functional neuroimaging, which generates maps of brain activity by detecting signals that correlate with the firing of brain cells. Functional neuroimaging usually involves the application of MRI or positron emission tomography (PET). The third type of neuroimaging, which typically employs PET, uses radioactive tracers to locate and quantify specific molecules in the brain. In research settings, imaging tools can help explain what goes wrong in the brain to produce certain mental illnesses, and these findings in turn can help define the boundaries of brain disorders. In clinical settings, neuroimaging tools may eventually play a role in diagnosis and in monitoring the effectiveness of treatment.

To be useful for psychiatric diagnosis, a test based on neuroimaging must be affordable and feasible to administer. It must also be sensitive enough to detect the inconspicuous features of a particular brain disorder and yet specific enough to rule out other conditions. Some anatomical signs of mental disorders are nonspecific: people with schizophrenia generally have enlarged cerebral ventricles (the fluid-filled spaces deep in the brain), but this abnormality may also occur in people with alcoholism or Alzheimer's. In patients with severe, chronic depression, the hippocampus—a brain structure critically involved in memory—may be atrophied, but

this anomaly has also been observed in post-traumatic stress disorder and is characteristic of the later stages of Alzheimer's. The utility of imaging for diagnosis will depend on finding abnormalities that are specific to a certain disease or perhaps to a symptom complex that may occur as a component of one or more diseases.

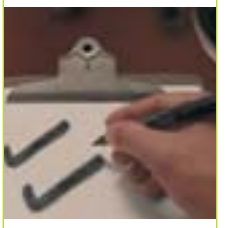
Furthermore, morphometric analysis of the human brain has proved to be challenging. Because the overall sizes and shapes of people's brains differ so much, researchers must employ complex computer algorithms to define normal values for various populations and compare the brains of individuals against those group norms. Moreover, the boundaries between brain structures may be very subtle. MRI atlases showing the anatomy of the normal human brain as it develops over the course of childhood and adolescence are only now becoming available.

Nevertheless, scientists have been able to use neuroimaging to shed some light on psychiatric illnesses. In 2001 teams led by Judith L. Rapoport of the National Institute of Mental Health and Paul Thompson and Arthur W. Toga of the David Geffen School of Medicine at U.C.L.A., produced an impressive study that found striking anatomical changes in the brains of adolescents with schizophrenia. The researchers focused on a relatively rare form of schizophrenia that begins in childhood. (The first signs of schizophrenia usually appear in the late teens or early 20s.) MRI scans of the brains of the affected children showed a remarkable loss of gray matter in the cerebral cortex—the brain structure responsible for higher thought—between the ages of 13 and 18 [*see illustration on page 101*]. As the disease progressed, the loss of gray matter intensified and spread, engulfing cortical regions that support associative thinking, sensory perception and muscle movement. The anatomical abnormalities mirrored the severity of the psychotic symptoms and the impairments caused by the disease.

Such studies point the way toward a diagnostic test. It is possible that some index of measurements of cortical thickness and the size of structures known to be affected in schizophrenia (such as the hippocampus) could be used to discern whether a young person is suffering from the disorder and to chart the progress of the disease. Early detection of schizophrenia could be a great boon to treatment. Researchers are now investigating whether early intervention in schizophrenia with antipsychotic drugs and stress management therapy can delay the onset of symptoms and reduce their severity.

Functional neuroimaging may also find significant uses in diagnosis. In Alzheimer's, loss of brain function may precede the macroscopic atrophy of brain structures. Investigators are already trying to refine the diagnosis for Alzheimer's by linking cognitive testing with functional imaging using MRI or PET. A similar strategy could possibly be applied to schizophrenia, which is characterized by failures in working memory (the ability to keep information in mind and manipulate it). It is conceivable that cognitive tests combined with functional imaging of the prefrontal cortex—a brain region that supports working memory—could contribute to the diagnosis of schizophrenia and, perhaps more important, track the success of therapy.

NEUROIMAGING TOOLS may eventually play a role in diagnosis and in monitoring the EFFECTIVENESS OF TREATMENT.



By combining neuroimaging with genetic studies, physicians may eventually be able to move psychiatric diagnoses out of the realm of symptom checklists and into the domain of objective medical tests. Genetic testing of patients could reveal who is at high risk for developing a disorder such as schizophrenia or depression. Doctors could then use neuroimaging on the high-risk patients to determine whether the disorder has actually set in. I do not want to sound too optimistic—the task is daunting. But the current pace of technological development augurs well for progress. SA

MORE TO EXPLORE

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