

12

Diagnosing Disorders

Psychiatric illnesses are often hard to recognize, but genetic testing and neuroimaging could someday be used to improve detection

STEVEN E. HYMAN

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 those of another. 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.

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 those of another.
- 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.

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 living 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 char-

acterized by discrete episodes of illness alternating with periods of relatively healthy mental function.

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 anti-anxiety 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, 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

acterized by discrete episodes of illness alternating with periods of relatively healthy mental function.

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 anti-anxiety 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, 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 about 50 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 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