

Brain Facts

NEW DIAGNOSTIC METHODS

MANY OF THE RECENT ADVANCES

in understanding the brain are due to the development of techniques that allow scientists to directly monitor neurons throughout the body.

Electrophysiological recordings, for example, the recording of auditory brainstem responses to assess hearing function in infants, trace brain electrical activity in response to a specific external stimulus. In this method, electrodes placed in specific parts of the brain — which vary depending on which sensory system is being tested — make recordings that are then processed by a computer. The computer makes an analysis based on the time lapse between stimulus and response. It then extracts this information from background activity.

Following the discovery that material is transported within neurons, methods have been developed to visualize activity and precisely track fiber connections within the nervous system. This can be done by injecting a radioactive amino acid into the brain of an experimental animal; the animal is sacrificed a few hours later, and then the presence of radioactive cells is visualized on film. In another technique, the enzyme horseradish peroxidase is injected and taken up by nerve fibers that later can be identified under a microscope.

These and other methods have resulted in many advances in knowledge about the workings of the nervous system and are still useful today. New methods, safely applicable to humans, promise to give even more precise information.

Imaging techniques

Positron emission tomography (PET) PET is one of the most important techniques for measuring blood flow or energy consumption in the brain. This method of measuring brain function is based on the detection of radioactivity emitted when positrons, positively charged particles, undergo radioactive decay in the brain. Small amounts of a radioisotope are introduced into the blood, which is then taken up into different brain areas in proportion to how hard the neurons are working. Computers build three-dimensional images of the changes in blood flow based on the amount of radiation emitted in these different brain regions.

PET studies have helped scientists understand more about how drugs affect the brain and what happens during various behaviors, such as learning and using language, and in certain brain disorders — such as stroke, depression, and Parkinson's disease. For example, PET allows scientists to measure changes in the release of some

neurotransmitters, which can be used to understand the relationship between a particular neurotransmitter and a behavior or cognitive process. Within the next few years, PET could enable scientists to identify the biochemical nature of neurological and mental disorders and to determine how well therapy is working in patients. For example, PET has revealed marked changes in the depressed brain. Knowing the location of these changes helps researchers understand the causes of depression and monitor the effectiveness of specific treatments.

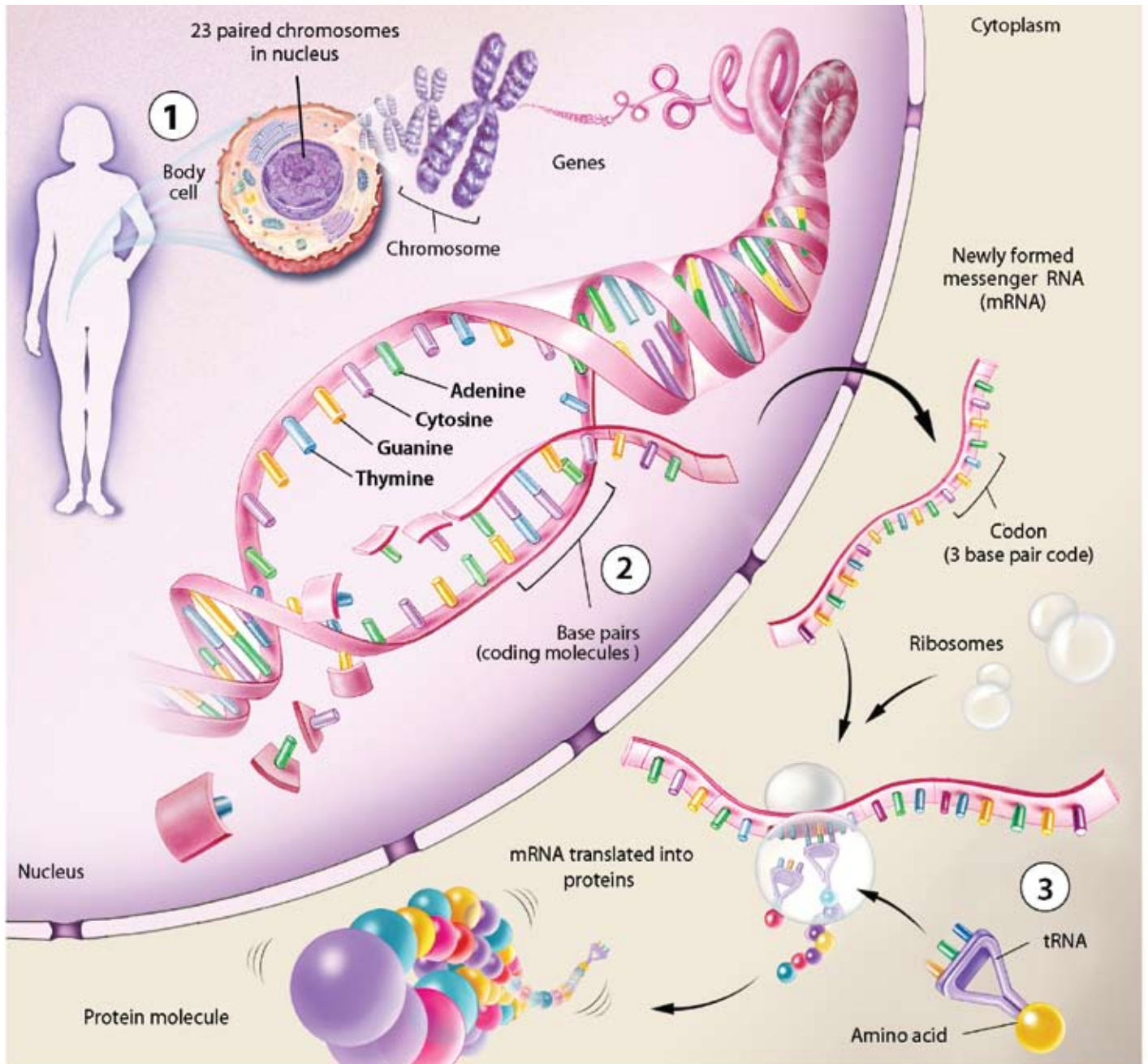
Another technique, *single photon emission computed tomography* (SPECT), is similar to PET, but its pictures are not as detailed. SPECT is much less expensive than PET because the tracers it uses have a longer half-life and do not require a nearby particle accelerator, typical of those used in nuclear physics, to produce them.

Magnetic resonance imaging (MRI) Providing a high-quality, three-dimensional image of organs and structures inside the body without X-rays or other radiation (noninvasive), MRIs are unsurpassed in anatomical detail and may reveal minute changes that occur over time.

MRIs tell scientists when structural abnormalities first appear in the course of a disease, how they affect subsequent development, and precisely how their progression correlates with mental and emotional aspects of a disorder.

During the 15-minute MRI procedure, a patient lies inside a massive, hollow, cylindrical magnet and is exposed to a powerful, steady magnetic field. Different atoms in the brain resonate to different frequencies of magnetic fields. In MRI, a background magnetic field lines up all the atoms in the brain. A second magnetic field, oriented differently from the background field, is turned on and off many times a second; at certain pulse rates, particular atoms resonate and line up with this second field. When the second field is turned off, the atoms that were lined up with it swing back to align with the background field. As they swing back, they create a signal that can be picked up and converted into an image. Tissue that contains a lot of water and fat produces a bright image; tissue that contains little or no water, such as bone, appears black.

A different MRI procedure can also assess the path of fiber tracts in the brain, that is, the connectivity between regions. This technology, referred to as *diffusion tensor imaging*, or DTI, takes advantage of diffusion rates of water, which tend to be higher along fiber tracts, to produce high-resolution images of how areas may connect in the brain.



CHROMOSOMES, GENES, AND PROTEINS. Every trait and chemical process in the body is controlled by a gene or group of genes on 23 paired chromosomes in the nucleus of every cell (1). Each gene is a discrete segment along the two tightly coiled strands of DNA that make up these chromosomes. DNA strands bear four different types of coding molecules — adenine (A), cytosine (C), guanine (G), and thymine (T) — the sequence of which contains the instructions for making all the proteins necessary for life (2). During protein production, a gene uses a molecule called mRNA to send a message with instructions for the amino acids needed to manufacture a protein (3).

MRI images can be constructed in any plane, and the technique is particularly valuable in studying the brain and spinal cord. It reveals the precise extent of tumors rapidly and vividly, and it provides early evidence of potential damage from stroke, allowing physicians to administer proper treatments early.

Magnetic resonance spectroscopy (MRS) MRS, a technique related to MRI, uses the same machinery but measures the concentration of specific chemicals — such as neurotransmitters — in different parts of the brain instead of blood flow. MRS also holds great promise: By measuring the molecular and metabolic changes that occur in the brain, this technique has already provided new information on brain development and aging, Alzheimer’s disease, schizophrenia, autism, and stroke. Because it is noninvasive, MRS is ideal for studying the natural course of a disease or its response to treatment.

Functional magnetic resonance imaging (fMRI) Among the most popular neuroimaging techniques today is fMRI. This technique compares brain activity under resting and active conditions. It combines the high-spatial-resolution, noninvasive imaging of brain anatomy offered by standard MRI with a strategy for detecting increases in blood oxygen levels when brain activity brings fresh blood to a particular area of the brain, which is a correlate for neuronal activity. This technique allows for more detailed maps of brain areas underlying human mental activities in health and disease. To date, fMRI has been applied to the study of various functions of the brain, ranging from primary sensory responses to cognitive activities. Given fMRI’s temporal and spatial resolution, and its noninvasive nature, this technique is often preferred for studies investigating dynamic cognitive and behavioral changes.

Magnetoencephalography (MEG) MEG is a recently developed technique that reveals the source of weak magnetic fields emitted by neurons. An array of cylinder-shaped sensors monitors the magnetic field pattern near the patient’s head to determine the position and strength of activity in various regions of the brain. In contrast with other imaging techniques, MEG can characterize rapidly changing patterns of neural activity — down to millisecond resolution — and can provide a quantitative measure of the strength of this activity in individual subjects. Moreover, by presenting stimuli at various rates, scientists can determine how long neural activation is sustained in the diverse brain areas that respond.

One of the most exciting developments in imaging is the combined use of information from fMRI and MEG. The former provides detailed information about the areas of brain activity in a particular task, whereas MEG tells researchers and physicians when certain areas become active. Together, this information leads to a much more precise understanding of how the brain works in health and disease.

Optical imaging techniques Optical imaging relies on shining weak lasers through the skull to visualize brain activity. These techniques are inexpensive and relatively portable. They are also silent and safe: Because only extremely weak lasers are used, these methods can be used to study even infants. In a technique called *near infrared spectroscopy* (NIRS), technicians shine lasers through the skull at near infrared frequencies, which renders the skull

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transparent. Blood with oxygen in it absorbs different frequencies of light from blood in which the oxygen has been consumed. By observing how much light is reflected back from the brain at each frequency, researchers can track blood flow. *Diffuse optical tomography* is then used to create maps of brain activity. A similar technique, the *event-related optical signal*, records how light scatters in response to rapid cellular changes that arise when neurons fire and potentially can assess neural activity lasting milliseconds. *Transcranial magnetic stimulation* (TMS) works by inducing electrical impulses in the brain by modulating magnetic fields — an electromagnetic coil that emits powerful magnetic pulses is held against the scalp. Repetitive TMS is being used to investigate the role of specific brain regions during behavior and can be combined with other neuroimaging techniques; for example, with fMRI, to establish a functional correlation between a region and a behavior.

Gene diagnosis

The inherited blueprint for all human characteristics, genes consist of short sections of *deoxyribonucleic acid* (DNA) sequence scattered throughout the long, spiraling, double-helix structure found on the 23 pairs of *chromosomes* in the nucleus of every human cell.

New hereditary linkage studies have made it possible to find the chromosomal location of genes responsible for neurologic and psychiatric diseases and to identify structural changes in these genes that are responsible for causing disease. This information is useful for identifying individuals who carry faulty genes and thereby improving diagnosis, for understanding the precise cause of diseases in order to improve methods of prevention and treatment, and for

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evaluating the malignancy of certain tumors and people's susceptibility to them.

So far, scientists have found the chromosomal location of defective genes for more than 100 neurological disorders and have identified the defect in up to 50. Prenatal or carrier tests exist for many of the most prevalent of these illnesses.

For example, scientists have tracked down the gene that goes awry in Huntington's patients. The defect is an expansion of a CAG repeat. CAG is the genetic code for the amino acid glutamine, and the expanded repeat results in a long string of glutamines within the protein. This expansion appears to alter the protein's function. Scientists have found that the size of the expanded repeat in an individual is predictive of susceptibility to and severity of Huntington's disease. Several other neurodegenerative disorders have been attributed to expanded CAG repeats in other genes. The mechanisms by which these expansions cause adult-onset neurodegeneration are the focus of intense research.

Sometimes patients with single-gene disorders are found to have a chromosomal abnormality — a deletion or break in the DNA sequence of the gene — that can lead scientists to a more accurate position of the disease gene. This is the case with some

abnormalities found on the X chromosome in patients with Duchenne muscular dystrophy and on chromosome 13 in patients with inherited retinoblastoma, a rare, highly malignant childhood eye tumor that can lead to blindness and death.

Gene mapping has led to the localization on chromosome 21 of the gene coding for the beta amyloid precursor protein that is abnormally cut to form the smaller peptide, beta amyloid. It is this peptide that accumulates in the senile plaques that clog the brains of patients with Alzheimer's disease. This discovery shed light on why individuals with Down syndrome with three copies of chromosome 21 (trisomy 21) invariably accumulate amyloid deposits; they make too much amyloid because they have an extra copy of this gene. Mutations in this gene have been shown to underlie Alzheimer's in another subset of these patients.

Gene mapping has enabled doctors to diagnose *fragile X mental retardation*, the most common cause of inherited mental retardation in males. Some scientists have now identified this gene, FMR1, which is found on the X chromosome and is important for neuronal communication. Other groups of scientists are investigating whether genetic components to schizophrenia, bipolar disorder, and alcoholism exist, but their findings are not yet conclusive.

Overall, the characterizations of the structure and function of individual genes causing diseases of the brain and nervous system are in the early stages. Factors that determine variations in the genetic expression of a single-gene abnormality — such as what contributes to the early or late start or severity of a disorder or prevents its occurrence in a mutant gene carrier — are still largely unknown.

Scientists also are studying the genes in *mitochondria*, structures found outside the cell nucleus that have their own DNA and are responsible for the production of energy used by the cell. Recently, mutations in mitochondrial genes were found to cause several rare neurological disorders. Some scientists speculate that an inheritable variation in mitochondrial DNA may play a role in diseases such as Alzheimer's, Parkinson's, and some childhood diseases of the nervous system.