BrainFacts

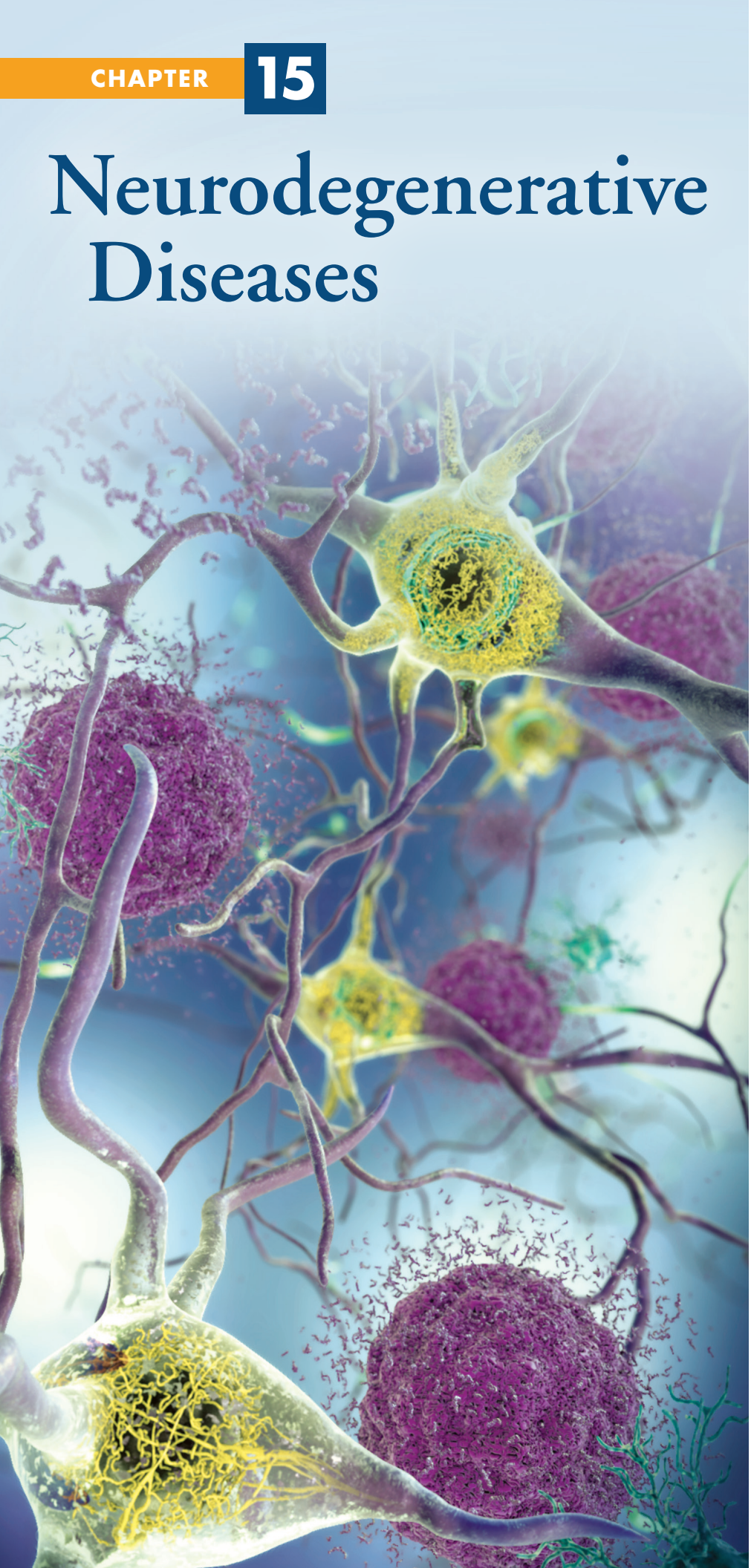
A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

Pages - 96 to end

A Companion Publication to *BrainFacts.org*

CHAPTER 15

Neurodegenerative Diseases



Neurodegenerative diseases all involve a progressive destruction of nerve cells. They more often affect older people, and are likely to become more common as life expectancy rises due to improved medical care — not only in the in the U.S. but worldwide. From 2015 to 2060, the number of people 65 and older in the U.S. is expected to jump from 48 million (15 percent of the population) to 98 million (nearly 25 percent of the population). As scientists look ahead, the field of neurodegenerative disease promises to become increasingly important.

In the past two or three years, articles in *Nature*, *Scientific American*, and other major science publications have discussed the intriguing possibility that many, if not all, neurodegenerative diseases involve misfolded proteins called prions. You may have heard of prions in the context of "mad cow disease." Scientists now wonder if prions also contribute to more familiar disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS, known as Lou Gehrig's disease). In the case of prions, a protein's normal 3-D structure has somehow been altered, so that it no longer functions correctly. Worse still, the misfolding can cause proteins to collect in irregular clumps that can damage cells. Is this really the cause of neurodegenerative diseases? Many scientists are asking that question. As you read this chapter, remember that there's still *a lot* to learn in this field — and each step toward understanding normal brain function aids the development of prevention or treatment for thousands of people in the future.

ALZHEIMER'S DISEASE

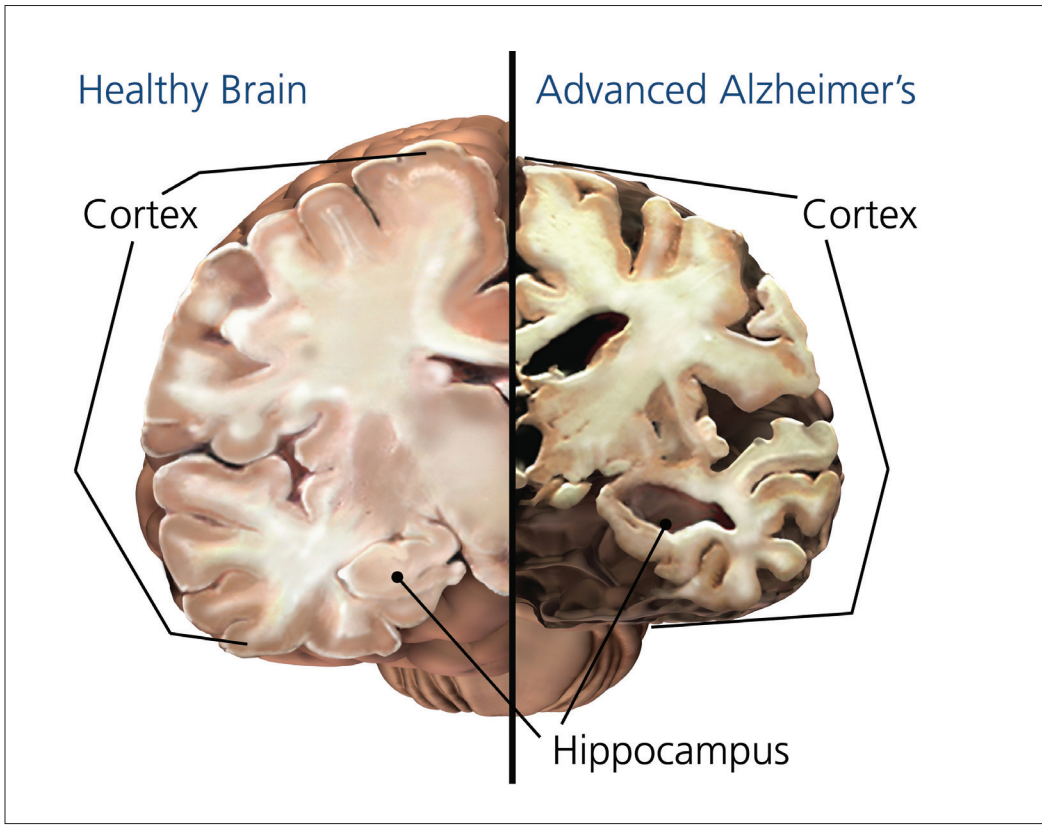
Alzheimer's disease is a form of dementia that is eventually fatal.

Over time, a person's brain undergoes irreversible, progressive degeneration that impairs his or her memory and reasoning. In the late-onset form of Alzheimer's, patients display symptoms in their mid-60s or later, with symptoms becoming more severe with age. In early-onset forms of the disease, patients can start to experience symptoms in their 30s. Fortunately, early-onset Alzheimer's occurs in less than 10 percent of cases of the disease.

Prevalence and Impact

Alzheimer's is the most common cause of dementia in older adults. Of the 47 million people with dementia worldwide, approximately 60 to 70 percent have Alzheimer's. The disease affects 5 to 8 percent of all people over 65 years of age, 15 to 20 percent above 75, and 25 to 50 percent of those over 85. It's estimated that more than 5 million people in the U.S. suffer from the disease; however, the actual number could be as high as 11 million, including many who are now asymptomatic. Conservative estimates are that Alzheimer's will affect 13.8 million people in the U.S. by 2050.

In 2014, Alzheimer's was the sixth leading cause of death in the U.S., accounting for 93,541 deaths. Deaths rose from 16.5 per 100,000 people in 1999 to 25.4 per 100,000 in 2014, but Alzheimer's-related deaths are believed to be severely underreported. Some patients go undiagnosed, and others have dementia-related conditions (such as aspiration pneumonia) rather than Alzheimer's listed as their primary cause of death. Some estimate that the number of Alzheimer's-related deaths might be six to seven times higher than reported. If this is accurate, it would be the third leading cause of death among older Americans.



Alzheimer's disease damages and destroys the connections between cells, causing widespread cell death. The damage causes problems with learning, memory, and thinking, and is eventually fatal.

Symptoms of Alzheimer's Disease

Alzheimer's symptoms are classified by the disease's progression. *Early stage* symptoms include memory problems (greater than expected in healthy people of a similar age), difficulty concentrating or finding appropriate words, problems judging and calculating, and disorientation in time or place. Most people are not diagnosed until the *mild stage* when symptoms include personality and behavior changes, wandering and getting lost, repeating questions, losing and placing objects in odd places, taking longer to complete daily tasks, and having trouble handling money and paying bills. In the *moderate stage*, some patients have trouble recognizing family and friends; inability to learn new things; problems coping with new situations; difficulty getting dressed or performing other multistep tasks; hallucinations, delusions, and paranoia; and impulsive behavior. In the *severe stage*, patients are completely dependent on others for care, as their body begins shutting down. Their communication is reduced to groans, moans, and grunts; sleeping increases; and they become bedridden. Other severe stage symptoms include weight loss, seizures, difficulty swallowing, skin infections, and a lack of bowel and bladder control.

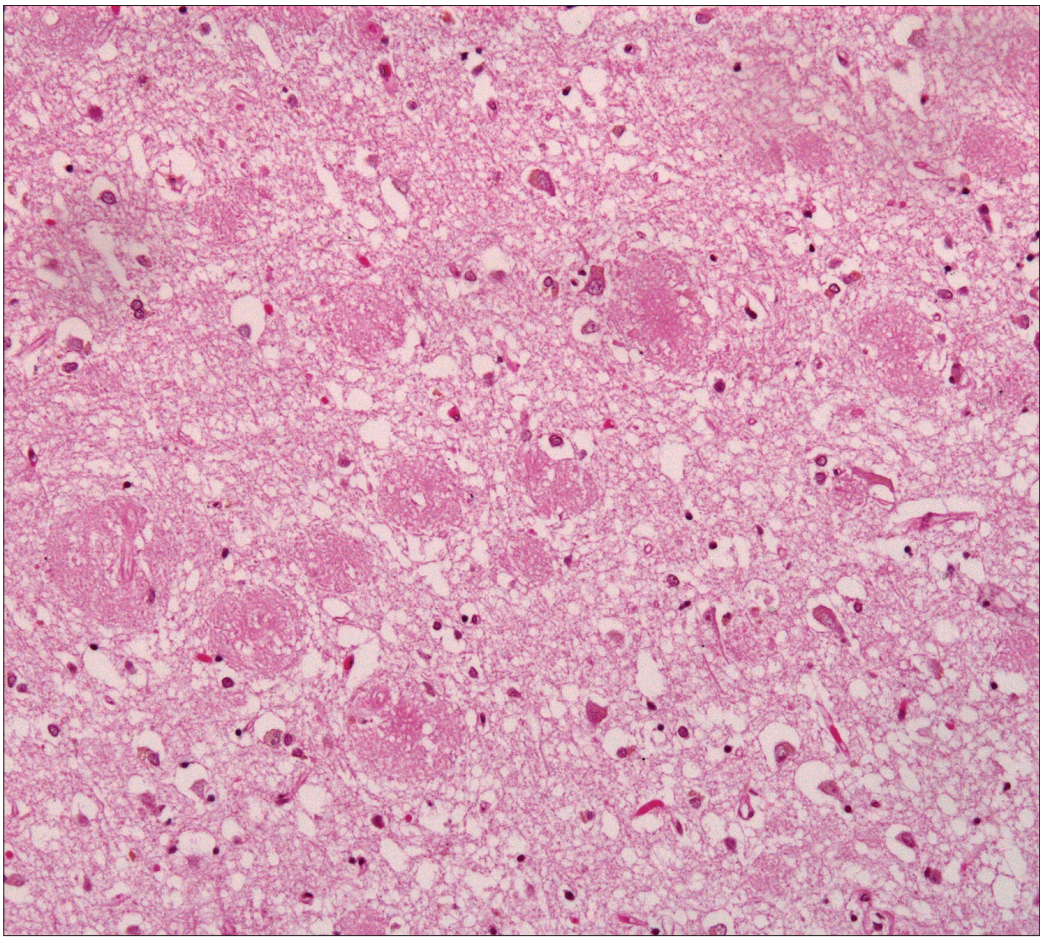
Diagnosing Alzheimer's

Alzheimer's dementia is most commonly diagnosed by a physician asking the patient and a family member or friend about the patient's

health, medical history, ability to perform daily activities, and changes in behavior and personality. Next, the physician conducts tests on memory, problem-solving, attention, counting, and language. Even if mental deficits are found, including dementia, the condition still might not be Alzheimer's. Similar deficits could be due to other conditions including Lewy body disease, frontotemporal dementia, Parkinson's disease, stroke, a tumor, sleep disturbances, side effects from medication, or infection.

Researchers are searching for a defining biomarker for Alzheimer's — a specific indicator that can physically identify a disease. Two candidate primary biomarkers are amyloid-beta (also called beta-amyloid) and tau. In Alzheimer's, amyloid-beta forms extracellular senile plaques, also known as neuritic plaques. These malformed clumps contain a fragment of the preliminary protein. In addition, tau, a type of protein that normally stabilizes the cellular skeleton, forms neurofibrillary tangles inside neurons. Both abnormalities are found in the brains of people with Alzheimer's but, at present, no definitive biomarker can diagnose the disease in its early stages. A diagnosis can only be confirmed by postmortem examination.

Some potential diagnostic methods for Alzheimer's include brain imaging, genetic risk profiling, and examining cerebrospinal fluid or blood. Neuroimaging, among the most promising areas of research focused on early detection, uses a mildly radioactive chemical marker that binds to amyloid plaques and shows their location in PET scans of living people. Starting in 2012, the FDA began approving the use of molecular imaging tracers to evaluate possible Alzheimer's disease or other causes of dementia. To date, the FDA has approved the use of three tracers — florbetapir F-18, flutemetamol F18, and florbetaben F18 — to detect amyloid-beta in the brain. However, neuritic plaques are also present in the brains of people with no dementia or Alzheimer's, so these scans are not used for routine evaluation.



Jensfloran.

Amyloid plaques, seen here as dark spots against pink brain tissue, are a hallmark of Alzheimer's disease. Scientists are still investigating whether plaques cause the disease or are merely a symptom of it.

Causes and Pathology

The causes and mechanisms underlying Alzheimer's disease are not fully understood. Most forms are likely caused by a combination of heredity, environment, and habits. Evidence has been building that head trauma is one contributing factor, based on a condition known as chronic traumatic encephalopathy (CTE) seen in football players and other athletes who play contact sports. Those with CTE typically show a buildup of tau protein in brain cells; some also have amyloid-beta deposits, but this is less common.

It appears that patients experience the first cellular changes associated with Alzheimer's a decade or more before becoming symptomatic. The neuronal transport system shows damage early in Alzheimer's. Patients produce fewer neurotransmitters — chemical molecules that are released from an axon terminal, travel across gaps called synapses, and transmit signals to another neuron, organ, or other tissue

type. In Alzheimer's disease, axons and synapses are damaged and ultimately destroyed. Damage to neuronal transport impairs attention, memory, learning, and higher cognitive abilities. While the cause is unknown, neuritic plaques and neurofibrillary tangles are the two prime suspects. Plaques consist of amyloid-beta, which is formed from malformed clumps of a fragment of amyloid precursor protein (APP), a fibrous protein often found at neuronal synapses. In its soluble form, amyloid-beta can bind strongly to neural receptors, which initiates the erosion of synapses. Evidence indicates that this soluble form is highly synaptotoxic, while the insoluble form (which has low toxicity) tends to aggregate, and is found in much higher concentrations than the soluble form. Some research suggests that the highly toxic, soluble form would be a better target for effective therapies.

The amyloid hypothesis is currently the dominant theory of how beta amyloid and tau protein interact to cause Alzheimer's. This hypothesis asserts that amyloid-beta starts a sequence of events that ultimately lead to Alzheimer's disease. Amyloid-beta accumulations first appear in the neocortex. Its neurotoxicity might be due to the fact that it exacerbates oxidative stress and damages the mitochondria, the cell's primary energy supply unit, initiating a cascade of neuronal dysfunction and cell death. The formation of neuritic plaques induces tau proteins to become defective and tangle into neurotoxic neurofibrillary tangles (hyperphosphorylated tau protein) within neuron cell bodies. (In contrast, normal tau protein stabilizes microtubules, which are crucial to axonal transport). Neurofibrillary tangles are generally first seen in the entorhinal cortex and the hippocampus, regions responsible for short-term memory and for transferring those memories to longer-term memory.

Although amyloid-beta and tau accumulations are found in people with Alzheimer's, there is no definite proof that they cause Alzheimer's. We *do* have evidence that tau and amyloid-beta might interact before clumping into their recognized disease forms. Even before it aggregates, malfunctioning tau can damage cellular transportation by blocking the microtubule tracks. Also, high tau levels can impair the function of amyloid-beta.

It's possible that inflammation and the presence of obesity can trigger these protein changes, increasing Alzheimer's incidence and severity. Plaques and tangles are known to negatively interact with microglia, non-neural brain cells that act as immune cells for the central nervous system, and astroglia, which offer physiological regulation and structural support in the brain.

Genetics of Alzheimer's

Early-onset Alzheimer's is a rare, dominantly inherited form of the disease. Dominant mutations in three genes — APP, PSEN1, and PSEN2 — cause early-onset familial Alzheimer's disease that starts when people are in their 40s and 50s. In late-onset Alzheimer's, the ApoE4 variant of the Apolipoprotein E (APOE) gene is a major genetic risk factor but not a determining one. The normal protein, ApoE, is mainly produced by astroglia or damaged neurons and helps clear soluble amyloid-beta from the brain.

In most people, Alzheimer's results from a combination of genetic and environmental causes. Several genetic associations have been noted. A mutant C9ORF72 gene has been found in people with both early- and late-onset forms of the disease. This gene codes for a protein that regulates transportation in the intracellular matrix. The mutation was already known to play a major role in ALS and frontotemporal dementia, but recent studies show that it also disrupts a key mechanism for DNA repair.

The TOMM40 gene, which codes for a protein responsible for moving proteins into mitochondria, has a complex relationship with Alzheimer's. People with a longer version of the gene were shown to be either predisposed or resistant to Alzheimer's — depending on whether a parent had the disease. Among those with an afflicted parent, people with the longer version of the gene were more apt to develop dementia than those with the shorter allele; but among those with *no* afflicted parent, people with a longer allele displayed better memory than those with a shorter gene allele.

With the TREM2 gene, loss-of-function mutations cause a sequence of physiological events associated with Alzheimer's disease. This suggests a possible genetic link between early- and adult-onset variants — the homozygous loss-of-function mutation is associated with early-onset and the heterozygous variant with adult-onset. Normally, TREM-2 protein helps regulate removal of cell debris, clearing amyloid proteins, and suppressing inflammation in microglia.

Two large programs are currently studying early-onset Alzheimer's. The Dominantly Inherited Alzheimer Network project is funded by the U.S. National Institute on Aging with 10 research centers in Australia, the United Kingdom, and the United States; and the Alzheimer's Prevention

Initiative is studying an extended family of 5,000 with the disorder in Antioquia, Colombia.

Treatments for Alzheimer's

The FDA has now approved five prescription drugs for treating Alzheimer's. While they relieve some symptoms, they do not cure or halt the disease. Three of these drugs are cholinesterase inhibitors: donepezil, galantamine, and rivastigmine. Cholinesterase inhibitors stop the action of acetylcholinesterase, an enzyme that breaks down the neurotransmitter acetylcholine. This increases the available amount of acetylcholine (involved in learning and memory), which counteracts the damaging effect of the disease on production of this neurotransmitter.

The fourth drug, memantine, is an NMDA receptor antagonist. Normally, NMDA receptors bind the neurotransmitter glutamate, allowing calcium to enter the neuron. In Alzheimer's, the damaged cells become overwhelmed with calcium, further damaging the neurons — a condition called neuronal excitotoxicity. Memantine blocks the flow of calcium through NMDA-receptor channels.

The fifth approved medication combines donepezil and memantine. Donepezil can be used in all stages of the disease, galantamine for mild to moderate stages, memantine for moderate to severe stages, and rivastigmine in all stages. The donepezil/memantine cocktail is used to treat moderate to severe Alzheimer's.

Several clinical trials are now underway to find new and better treatments for Alzheimer's. The Alzheimer's Forum currently lists 14 treatments that are in the later stages of clinical trials. Overall, however, there is a high failure rate for drugs on the road to approval. Between 2002 and 2012, just 0.4 percent (1 in 245) of Alzheimer's drugs were approved. Potential drugs have often proved ineffectual because they don't target Alzheimer's early pathology. Online registries may improve the situation by hastening participant recruitment for clinical trials and looking for people at ever-earlier stages of disease progression. Trials are also broadening their pool of participants to include people likely to develop Alzheimer's but currently asymptomatic, as well as other participants at the pre-dementia stage.

Another treatment strategy, based on the amyloid hypothesis, uses the body's immune response to attack and clear amyloid plaques. Trials for active immunization (which trains the immune system to build a person's antibodies) and passive immunization (which transfers already active defensive antibodies without bolstering the person's own immune system) have both been explored. So far, however, these types of therapies have been inadequate for people with moderate to severe symptoms.

PARKINSON'S DISEASE

Parkinson's disease is the second most common neurodegenerative disorder in humans. Like Alzheimer's, its incidence increases with age, with the average onset around age 60. About 5 million people in the world's 10 most populous countries have Parkinson's, and its frequency is expected to double by 2030. With 50,000 to 60,000 cases diagnosed annually in the U.S., the actual figures may be much higher — especially since early symptoms can be mistaken for normal aging and thus are not reported.

From 2000 to 2013, the age-adjusted death rates for those with Parkinson's disease increased in the U.S. from 8.8 to 11.0 per 100,000 for males and from 3.9 to 4.8 per 100,000 for females. For reasons not yet understood, the disease is more prevalent in men than in women. Five to 10 percent of cases are "early-onset," occurring before age 50. Rarer still, patients with "juvenile Parkinsonism" may develop symptoms before age 20.

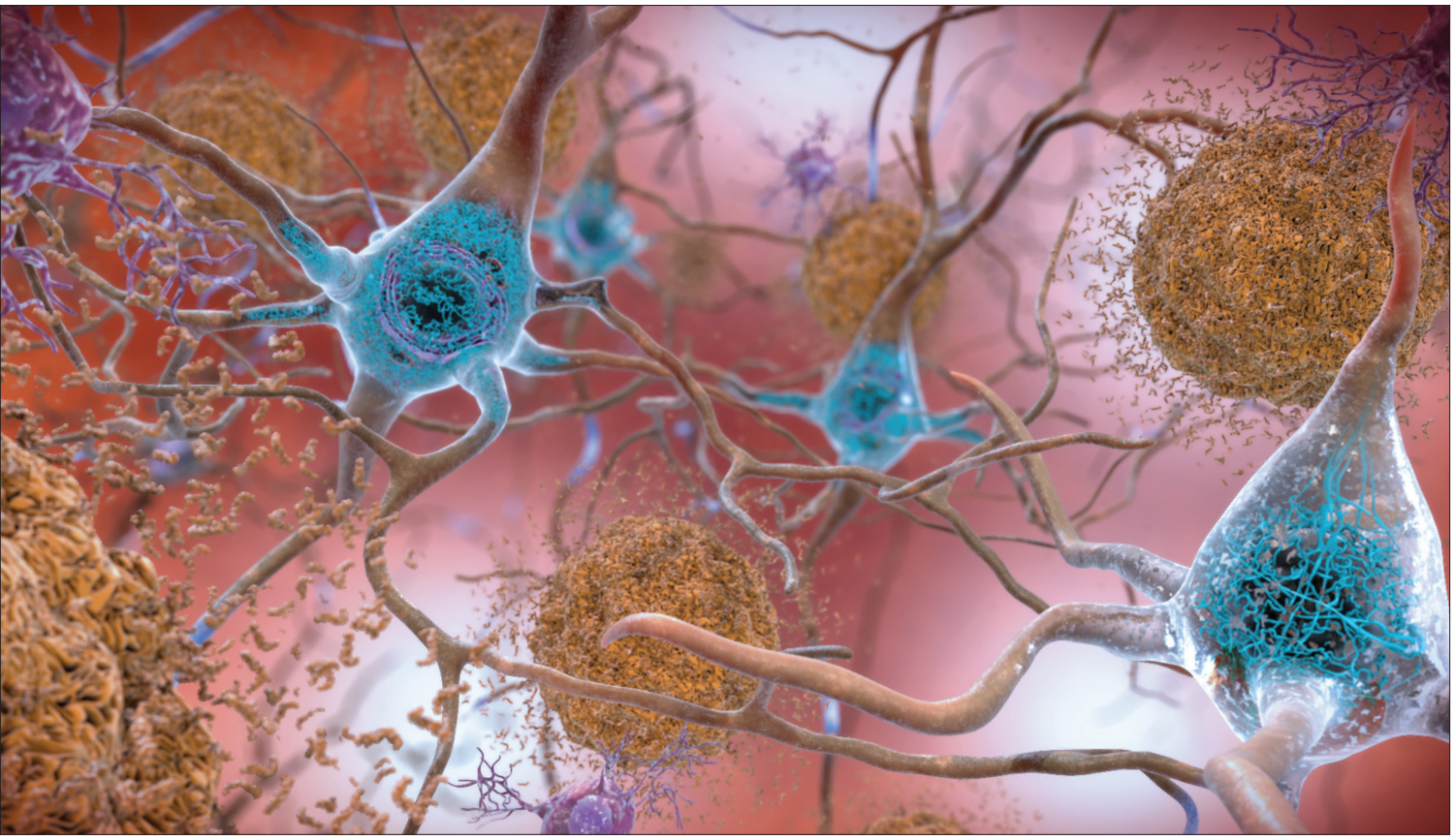
Estimates of the prevalence, or overall number, of Parkinson's patients vary widely, so incidence — the occurrence of new cases within a given time period (for example, per year) — is a better index for this disease. There is a higher incidence of Parkinson's in developed countries but the reason is unknown, although increased risk of the disease has also been reported in rural areas with increased pesticide use.

Symptoms

At first, Parkinson's is characterized by motor problems: slow movement; muscular rigidity; poor coordination and instability; and shaking in hands, arms, legs, jaw, and face while at rest. As the disease progresses, the shaking, known as resting tremor, may worsen and interfere with walking, talking, and other simple tasks. Cognitive decline often occurs at later stages. Some people develop depression and other emotional changes, difficulty swallowing and chewing, skin problems, constipation or urinary problems, and sleeping problems. However, the rate and intensity of Parkinson's progression vary. Some people become severely disabled, while others have only minor motor disruptions.

Pathology and Causes

Parkinson's is a motor system disorder caused by the loss of dopamine-producing cells neurons



National Institute on Aging, NIH.

Alzheimer's disease is associated with high levels of the beta-amyloid protein. This protein clumps together and forms plaques, which are pictured in brown. These plaques can build up between neurons and interrupt their activities. Tau proteins also accumulate and form tangles — seen in blue — within neurons, disrupting communications.

in the substantia nigra — a midbrain structure that is considered part of the basal ganglia. This brain region affects movement, reward, and addiction. At the cellular level, the death of neurons likely arises as a result of damage to mitochondrial respiration.

Some early-onset cases are linked to mutations in the PARK2 (or PRKN) gene, which codes for the protein "parkin." Most types of Parkinson's are caused by a combination of genetics and environment, but an estimated 15 to 25 percent of people with adult-onset Parkinson's have a known relative with the disease. Genes like alpha-synuclein (SNCA), repeat kinase 2 (LRRK-2), and glucocerebrosidase (GBA) also point to the importance of genetics as a causal factor. While Parkinson's and Lewy body dementia are sometimes considered different disorders, Lewy bodies, accumulations of proteins in neuron bodies, have been implicated in both diseases. Lewy bodies are mainly composed of the protein alpha-synuclein entangled with other proteins, including neurofilament, ubiquitin, alpha B crystallin, and probably tau protein in neurofibrillary tangles. The Lewy body protein, alpha-synuclein, is involved in dopamine transport in the nervous system.

There is no definitive test for Parkinson's so, without accepted biomarkers, diagnosis is based on medical history and neurological tests that can include brain scans. Accurate diagnosis can be difficult, because some non-Parkinson's conditions display similar symptoms. In the future, mitochondrial molecules could be a potential source of a Parkinson's biomarker.

Research

Scientists can treat mice with the chemical MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) to create an animal model that can provide further insight into Parkinson's. In the body, MPTP metabolizes into the neurotoxin MPP+ (1-methyl-4-phenylpyridinium), which causes a Parkinson's-like loss of cells in the substantia nigra and cognitive deficits. However, MPTP does *not* perfectly mimic the symptoms of human Parkinson's disease, including the motor deficits.

Research on using stem cells to replace damaged dopamine neurons

in Parkinson's patients has shown promise. There are two types of stem cells: the more flexible (and controversial) fetal tissue and induced pluripotent stem (iPS) cells, which are specialized adult (often blood or skin) cells that have been repurposed into a generalized embryonic state. There have been successful lab studies using iPS cells, and positive to mixed results in clinical studies with the fetal stem cells. A Kyoto University study, published in August 2017, transferred human iPS cells into the brains of monkeys treated with MPTP. Two years after this transplantation, the treated monkeys were shown to have healthy DA neuron integration, growth, and even functioning in the striatum.

Treatments

Treatment with levodopa (L-Dopa) temporarily relieves Parkinson's motor symptoms but does not slow disease progression. Ironically, the long-term use of L-Dopa can induce dyskinesia — abnormal and uncontrolled involuntary movements. Strategies for treating Parkinson's include gene therapy and targeting specific cellular molecules.

A surgical procedure called deep brain stimulation (DBS) is increasingly used to treat Parkinson's patients whose symptoms, including rigidity, tremor, slowed movement, and mobility problems, do not respond adequately to medication. The DBS technique implants a small neurostimulator device — like a pacemaker — that sends electrical impulses that interfere with and block brain signals that cause the motor symptoms of Parkinson's. Before implanting a neurostimulator into the brain, the neurosurgeon locates where the patient's symptoms are originating, using MRI or CT scans. Most often, the problem areas in the brain are the thalamus, the subthalamic nucleus, and a portion of the globus pallidus (part of the basal ganglia). After the imaging, microelectrode recording — which involves a small wire that monitors the activity of nerve cells in the target area — is sometimes used to further localize problem areas in the brain. This approach has proven to be highly successful with a segment of patients.

One treatment still in the research stage is a strategy to break apart Lewy bodies. The idea is to use high hydrostatic pressure to break apart aggregated alpha-synuclein fibril plaques, like those found in Lewy bodies, and return the protein to its properly functioning form. Another novel approach to preventing Parkinson's was suggested by epidemiological studies that found that the disease is less common among coffee drinkers and cigarette smokers. If caffeine and nicotine offer protection, this could reflect some central action that benefits the brain's dopaminergic systems.

AMYOTROPHIC LATERAL SCLEROSIS

ALS is a group of progressive, ultimately fatal motor neuron diseases. ALS is also called Lou Gehrig's disease after the renowned New York Yankee first baseman, who was one of the most famous victims of the disease. ALS forced Gehrig to retire at age 36. Gehrig died two years later. ALS afflicts as many as 15,000 Americans, most between the ages of 50 and 70. Although men are slightly more likely than women to develop the disorder, that difference lessens with increasing age. For unknown reasons, non-Hispanic whites are more likely than other ethnicities to develop ALS. Military veterans' likelihood of developing the disease is as much as 1.5 to 2 times higher than the rate in the general population — possibly due to exposure to environmental toxins like lead and pesticides.

ALS is also called Lou Gehrig's disease after the renowned New York Yankee first baseman, a famous patient with the disease.

Symptoms

Unlike the previously discussed neurodegenerative disorders, generally neither cognition nor personality is affected in individuals with ALS. Early ALS symptoms include muscle

weakness, twitching, and eventual paralysis in the hands and feet. These symptoms gradually spread as patients lose strength and the ability to move, speak, and eat. Most ALS patients die within three to five years after symptoms appear due to nerve damage affecting the respiratory muscles. However, 10 percent of ALS patients — like the physicist Stephen Hawking — survive 10 years or more.

Pathology and Causes

Motor neurons connect the brain to the spinal cord and to the voluntary muscles throughout the body. In ALS, the motor neurons degenerate and then die. Without this neural communication, a person's voluntary muscles weaken, begin twitching, and finally atrophy.

Only 5 to 10 percent of ALS cases are due solely due to genetic factors — a condition called "familial ALS"; the non-familial disease is called "sporadic ALS." While several genes have been identified that increase susceptibility to ALS, there is no clear pattern of inheritance. Among cases with a genetic component, about 25 to 40 percent are caused by a harmful mutation in the C9ORF72 gene. Some individuals with this mutation show symptoms of both motor neuron and dementia disorders, a condition known as ALS-FTD (ALS-frontotemporal dementia). Another 12 to 20 percent of hereditary cases result from mutations that prevent the SOD1 gene from coding for superoxide dismutase — an enzyme that catalyzes the breakdown of cell-damaging superoxide radicals into more benign molecular oxygen or hydrogen peroxide. These and other hereditary forms of ALS, such as those involving UBQLN2 and VEGF genes, provide valuable insights into the mechanics of the disease.

Research and Treatments

There is no cure for ALS, nor has any medication been found that can stop or reverse its progression. But the FDA has approved edaravone and riluzole for treating ALS. Edaravone, an antioxidant that inhibits the production of cell-damaging free radicals, can ameliorate disease symptoms. Riluzole decreases glutamate levels, and has been shown clinically to extend the life of ALS patients by a few months.

A therapy called NurOwn, developed by BrainStorm Cell Therapeutics, is entering a phase 3 clinical trial (to confirm drug safety and efficacy over a longer testing time) after showing promise for halting or reversing ALS progression. NurOwn uses undifferentiated stem cells from the patient's own bone marrow, which are then modified to boost the production of neurotrophic factors that support and protect neurons destroyed by the disease.

For those with the *SOD1* mutation, there is also hope for a gene silencing technique using an artificial RNA snippet. Lab tests in mouse models have preserved muscle strength and motor and respiratory functions, and delayed disease onset and death. This treatment has also safely silenced SOD1 in the lower motor neurons of nonhuman primate models.

Participation in a multidisciplinary ALS clinic, an ALS Association Certified Treatment Center of Excellence, or a Recognized Treatment Center can also improve ALS patients' quality of life.

HUNTINGTON'S DISEASE

Huntington's disease (HD) is a heritable disease that impairs voluntary movement and cognition. The disease afflicts 3 to 7 people of 100,000 people of European descent, but is less common among Japanese, Chinese, or African populations. The HD variant of the HTT gene is dominant; if one parent has a single copy of the HD gene variant and the other parent has normal HTT genes, a child has a 50 percent chance of inheriting the HD variant and developing the disease. The most common form of HD begins earlier than most progressive brain diseases, becoming active when people are in their 30s and 40s. Death occurs 15 to 20 years after a patient becomes symptomatic. Juvenile HD begins in childhood or adolescence, and juvenile HD patients usually die 10 to 15 years after their symptoms appear.

Symptoms

Signs of HD begin with irritability, mood swings, depression, small involuntary movements (called chorea), poor coordination, and difficulty making decisions and learning new information. As the disease progresses, the chorea becomes more pronounced and patients have increasing trouble with voluntary movements like walking, speaking, and even swallowing. Their cognitive problems also worsen. While juvenile HD displays the same symptoms as the more common form, it also includes slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired, and seizures occur in 30 to 50 percent of children with this condition.

Causes and Genetics

In 1993, Huntington's disease was found to be caused by mutations in the HTT gene, which codes for the huntingtin protein, located on chromosome 4. The protein likely interacts with other proteins involved in

signaling, transport, binding to proteins and other structures, and protecting the cell from self-destruction. The disease mutation involves an abnormal number of repeats of a three-part (trinucleotide or triplet) snippet of DNA in the HTT gene. This sequence of the nucleotides cytosine, adenine, and guanine (CAG) normally repeats 10 to 35 times, but occurs from 36 to 120 or more times in the mutation. The greater the number of CAG repeats, the earlier symptoms appear and the more severe they are.

The "expanded" huntingtin protein is susceptible to clumping. While aggregated huntingtin proteins don't cause cell death directly, they disrupt the mitochondrial electron transport chain, initiating a cascade of neuronal dysfunction and death. Brain areas most often affected are the basal ganglia (voluntary movement) and the cortex (cognition, perception, and memory).

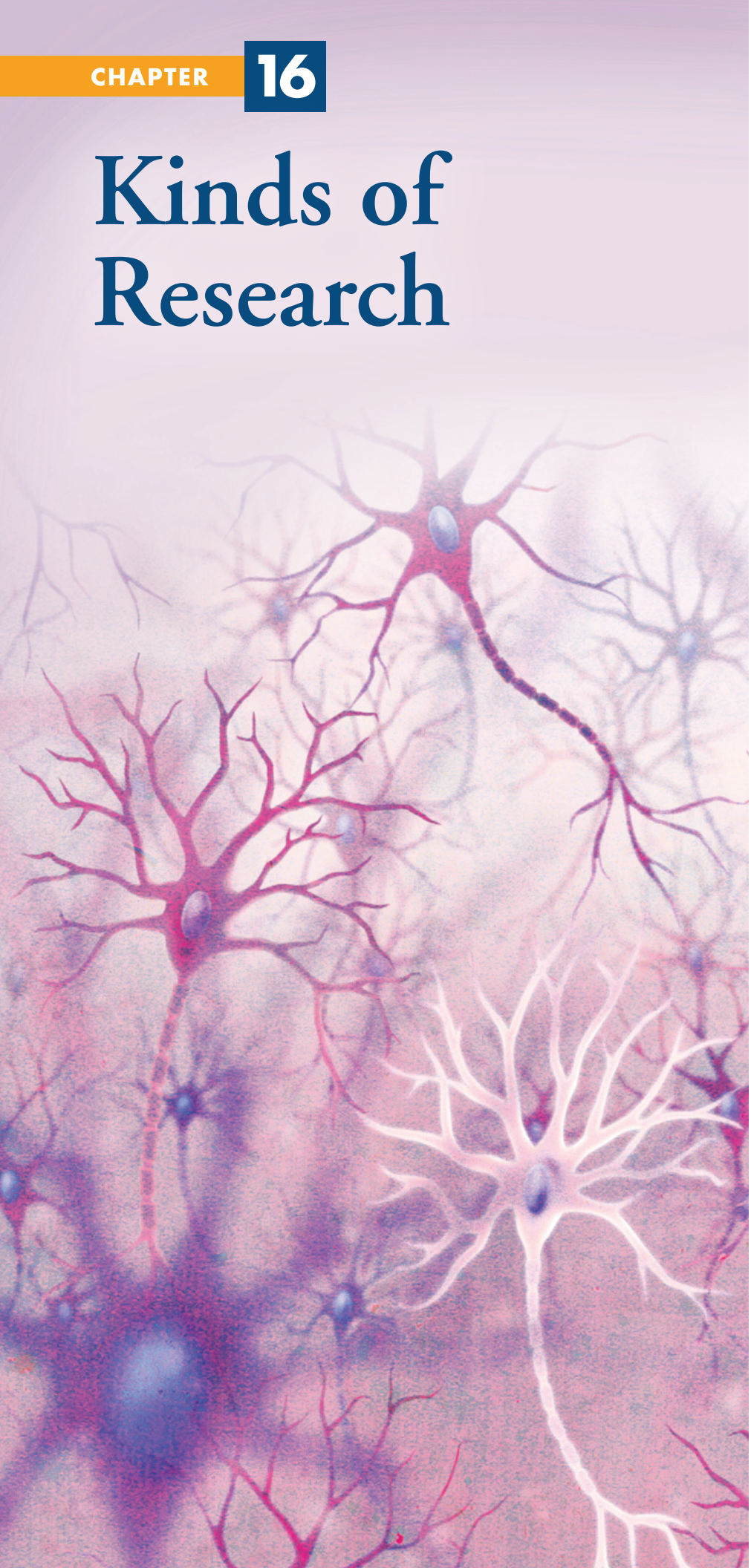
Detection and Treatments

In late 2015, Ionis Pharmaceuticals began the first human trials of a "gene silencing" or "huntingtin lowering" drug. IONIS-HTTRx is an antisense oligonucleotide — a single strand of a chemically modified DNA designed to interrupt and decrease the mutated form of the huntingtin protein produced in HD patients. The drug is now in phase 2 trials comparing it to a placebo in early-stage HD patients who are randomly assigned to treatment or control groups.

In spring 2017, the FDA approved the drug deutetrabenazine for treating chorea associated with Huntington's disease. This is reportedly only the second product approved for treating HD. Furthermore, there is now evidence for viable HD biomarkers. Tau (which turns up regularly in neurodegenerative diseases) and neurofilament light chain, a component of the neuronal cytoskeleton, are found at elevated levels in cerebrospinal fluid of HD patients. A recent study points to the neurofilament light chain, and to a lesser extent tau, as viable HD biomarkers. Interestingly, the neurofilament light chain is also being investigated as a biomarker for ALS and other neurodegenerative diseases. In mouse studies, the amount of neurofilament light chain found in the animals' cerebral spinal fluid and blood increased before neurological signs appeared, likely coinciding with the development of brain lesions.

CHAPTER 16

Kinds of Research



As you've seen in previous chapters, neuroscientific research has made astounding advances in the past 150 years. The development of new research tools and technologies has driven these discoveries, from the first images of individual neurons to revealing the genetic causes of neurological disorders. This chapter introduces you to some of the most important research methods used to understand the brain, including unusual types of microscopy, animal models, and cutting-edge molecular techniques.

TOOLS FOR ANATOMY

Anatomy is the study of structure — most often, the structure of biological organisms. For the brain, anatomy starts with the structure of neurons, which are among the most complex and diverse cell types in our bodies. Scientists were first able to observe neurons in the late 19th century, thanks to histological techniques that start with a very thin slice of brain tissue to which scientists apply stains or other compounds that add contrast or color to specific structures. They then view the tissue with a light microscope, which passes visible light through the thin slice and lenses that make the structures look up to 1,000 times larger than they do with the naked eye.

Histology is the study of how cells form tissues. Histological techniques can reveal changes in the density of cell types or the presence of molecules that can suggest a particular disease. These techniques have helped illuminate the brain changes underlying some neurodegenerative disorders. For example, histological methods have shown that an enzyme that breaks down acetylcholine is associated with

the brain plaques and tangles of Alzheimer's disease. And in the brains of Parkinson's disease patients, histology has revealed the death of neurons that normally control movements through dopamine signaling.

Long after light microscopes gave scientists their first glimpses of neurons, a debate bubbled in the scientific community: Are neurons individual cells or a mesh of physically interconnected cell bodies? Neurons are so densely packed that the answer wasn't clear until the 1950s, after the development of a new technology called electron microscopy. Electron microscopes can produce useful detailed images of cellular structures magnified many 100,000s of times by directing a beam of electrons through very thin slices of tissue, then enlarging and focusing the image with electromagnetic lenses. With this technology, researchers were finally able to see that neurons are not physically continuous but, instead, are individual cells.

Although they are individual cells, neurons do act in networks, communicating across small gaps called synapses, where the axon terminal of one cell meets a dendrite or cell body of another cell. One method for mapping the signaling pathways within these networks involves injecting radioactive molecules or "tracers" into the cell body of a neuron. Researchers monitor the movement of radioactivity down the neuron's axon, showing where that neuronal path leads. A similar technique involves tracers that can actually travel across synapses, from one neuron to the next. Scientists have used such tracers to map the complex pathways by which information travels from the eyes to the visual cortex.

Another technique for examining brain anatomy is magnetic resonance imaging, or MRI. Developed in the 1980s, MRI is widely used by researchers and doctors to view a detailed image of brain structure. MRI equipment uses radio waves and strong magnets to create images of the brain based on the distribution of water within its tissues. MRI is harmless and painless to the person being scanned, although it does require sitting or lying in a narrow tube, and the procedure can be quite noisy. With an MRI scan, researchers can tell the difference between the brain's gray matter and white matter. Gray matter consists of the cell bodies of neurons, as well as their dendrites and synapses. White matter mostly contains axons wrapped in the fatty myelin coating that gives these regions their white color. Based on the distribution of water in the tissues, MRI images clearly differentiate between cerebrospinal fluid, the water-rich cells of gray matter, and fatty white matter.

TOOLS FOR PHYSIOLOGY

Information is conveyed along the neuronal pathways that crisscross through our brains as electrical activity traveling down axons. To study this activity, researchers measure changes in the electrical charge of individual neurons using techniques of electrophysiology. A thin glass electrode is placed inside a neuron to measure the voltage across its cell membrane, which changes when the neuron is activated. This technique can measure neuron activity inside the brains of living lab animals such as rats or mice, enabling scientists to study how neurons transmit electrical information in their normal physical context. Alternatively, a slice of brain can be kept "alive" for a short time in a Petri dish, if the right environment (temperature, pH, ion concentrations, etc.) is provided. In an isolated brain slice, researchers can better identify the exact cell they are recording from and can infuse drugs into the Petri dish to determine their effects on the brain.

Using these methods, scientists have made critical discoveries about synaptic plasticity — the capacity of a synapse to become stronger or weaker in response to sensory inputs or other activity. For example, repeatedly stimulating a neuron by training an animal in a particular task, or by direct electrical stimulation, increases the synaptic strength and the chance that the downstream neuron will react to the incoming signal.

A disadvantage of electrophysiology, as described above, is that the techniques are highly invasive. However, another method, called electroencephalography or EEG, is able to record human brain activity without invasive or harmful procedures. In EEG, about 20 thin metal discs are placed on the scalp. Each disk is connected by thin wires to a machine that records the activity of neurons near the brain surface. This approach has been especially useful for understanding epilepsy and the stages of sleep. However, it does not provide information at the level of individual neurons.

Researchers who need to look at individual neurons in a living brain can use a technique called two-photon microscopy. A lab animal such as a fly or mouse must be genetically modified so that some of its neurons produce a protein that glows when a laser beam shines on them. Two-photon microscopy has enabled scientists to understand changes in the brain during normal processes like learning, as well as changes that occur over the course of a disease — for example, watching how the branches on

neurons near Alzheimer's-like plaques break down over time.

TOOLS FOR GENETICS

The human genome is made up of 3 billion pairs of DNA letters or "bases." This multitude of adenine (A), cytosine (C), guanine (G), and thymine (T) bases comprises an estimated 20,000 genes that spell out instructions for making proteins, along with regulatory and other non-coding DNA regions whose functions are not fully known. Scientists study genetics in many ways, such as following diseases or other traits through family pedigrees or identifying the exact order of DNA bases (the DNA "sequence") that code for a given trait. More recent genetic tools enable scientists to manipulate genes and other genetic features to better understand how the brain works and how to treat it in cases of dysfunction or disease.

Scientists often don't know which gene or other DNA feature controls a trait. At the outset, a particular trait could be encoded on any of the 23 pairs of chromosomes in a typical human cell. But with genetic linkage studies, researchers have begun to map gene locations. First, researchers must identify another trait with a *known* chromosomal location that tends to be inherited with or "linked" to the trait of interest. This technique, which narrows down the likely location of the gene of interest, was the first step toward identifying the genetic basis of many neurological disorders.

When you think about mutations, you probably think of harmful changes in one or several DNA bases within a gene. But some disorders result from an overabundance of copies or repeats of a stretch of DNA. This is the case with Huntington's disease. The normal HTT gene has about a dozen repeats of a small stretch of DNA within the gene, but Huntington's patients can have more than 100 of these repeats. Researchers now use DNA chips or microarrays to identify such variations in copy number. The "array" of a microarray refers to the thousands of spots arrayed in rows and columns on the surface of the chip; each spot contains a known DNA sequence or gene, which can grab onto corresponding bits of the genome being analyzed. Using this tool, scientists are able to compare DNA samples of two people, perhaps one healthy and one with a disorder, to see if certain pieces of DNA are repeated more in one person than in the other. Another type of microarray helps researchers determine if a patient has a chromosomal translocation — a chunk of a chromosome that has been misplaced onto another chromosome.

Recent years have seen great advances in DNA sequencing methods, allowing researchers to more efficiently and affordably explore the exact DNA sequence that might underlie brain disorders. In the early 2000s, the Human Genome Project made public the vast majority of the human genome sequence; in the years that followed, the science of genomics has enhanced scientists' understanding of brain function at the level of genes, cells, and circuits. Genomics can help identify genetic variations that cause conditions ranging from depression to schizophrenia to movement disorders.

Genetics research now goes far beyond reading the sequence of bases in the genome. In the last few years, scientists have harnessed a molecular tool that can edit the genome more precisely and efficiently than was previously possible. This tool, called CRISPR (which stands for Clustered Regularly Interspaced Short Palindromic Repeats), evolved as a bacterial immune system that targets viral invaders. Scientists have harnessed CRISPR's components to home in on specific DNA sequences in lab animals and human cell cultures. By tethering DNA-cutting enzymes to this targeting system, scientists can recreate mutations found in patients with neurological disorders, or even insert new bits of DNA to test their effect. With CRISPR, scientists have been able to mimick Alzheimer's in rodents, in order to study the disease and its potential treatments. CRISPR is also used to study mutated human neurons in Petri dishes. Researchers can observe how mutations that cause autism, Parkinson's disease, or other conditions affect neuronal growth and function.

Optogenetics is another fascinating intersection of genetic tools with brain science. This ingenious technique allows researchers to control brain activity with flashes of light. Scientists genetically modify a lab animal like a mouse so that its neurons produce a light-responsive protein. Then, optical fibers are inserted into the brain to allow light to shine on those neurons — either activating or silencing them. Optogenetics has helped scientists better understand how neurons work together in circuits. This technique has also been used to control animal behaviors ranging from sleep to drug addiction.

Oddly enough, genetics is not always about genes. As mentioned above, much of the human genome contains DNA sequences that are not genes, whose job is to regulate gene activity. These regulatory sequences,

and the enzymes that make changes to them, help determine under what conditions (in what cells, at what age, etc.) a gene is expressed or repressed. These epigenetic changes occur in cells when chemical tags are placed on the regulatory regions of certain genes; the tags influence whether those genes will be turned on or off. In the past decade, epigenetics research has begun to clarify the role of gene regulation in brain development and learning. Epigenetics has also revealed how mutations in the regulatory regions of DNA can cause disease, just as mutations can in genes.

Genetics in Neurological Diseases

The impact of mutations varies from person to person, and from disease to disease. A particular mutation might explain some cases of a disorder but not others, or it could be only one of several genetic changes affecting a patient. Lissencephaly is a brain malformation in which the surface of the brain is smooth, unlike normal brains whose surfaces have ridges and grooves. It affects development. Babies with lissencephaly start having spasms in the first months of life and develop drug-resistant epilepsy and severe intellectual and motor disabilities. Although about 70 percent of these patients have mutations in the LIS1 gene, at least two other mutations have been associated with the condition. Another complex genetic condition, Kabuki syndrome, is marked by intellectual disabilities, a distinctive facial appearance, slow growth in infancy, and other physical problems. Kabuki syndrome is hard to diagnose because some symptoms, such as intellectual disability, range from mild to severe. DNA sequencing has found that most patients, but not all, have mutations in the KMT2D gene — and some patients carry the mutations in only some of their cells. In addition, people with Kabuki syndrome may have mutations in other genes that function like KMT2D.

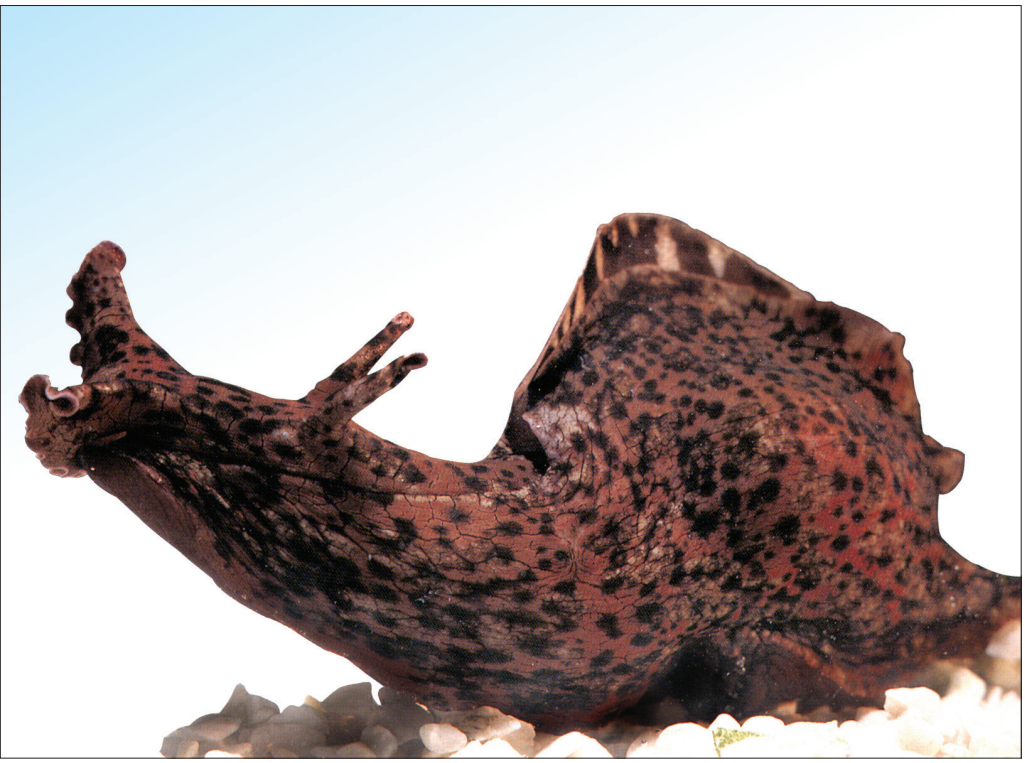
It is also possible for a person to carry a mutation but exhibit no outward signs. Fragile X syndrome, the most common form of congenital intellectual disability in males, is caused by an excessive number of DNA sequence (CGG) repeats within the FMR1 gene. The protein product of the FMR1 gene, which is important for synapse function, is disrupted by these repeats. While some people with elevated numbers of the sequence repeats may not be affected, they are carriers with a risk of passing it on to their children.

TOOLS FOR BEHAVIOR

To understand how brain function drives behaviors in humans, researchers often turn to animal models. An eight-inch long marine slug may not look like a very promising model of brain function but, over the years, the animal known as *Aplysia* has helped scientists uncover many principles of learning and memory. *Aplysia* has relatively few neurons (around 10,000, compared to approximately 86 billion in humans), but some of its neurons are large enough to be seen with the naked eye. *Aplysia* also exhibits simple behaviors that can be modified with training. For example, *Aplysia* will reflexively withdraw its gill after receiving an electric shock to its tail. It can be trained to withdraw its gill in response to an innocuous touch which, during training, was paired with an electric shock. Scientists have discovered how the timing of training sessions affects learning, and have identified proteins and other molecules that strengthen synapses so the neuronal response is greater the next time *Aplysia* is stimulated. Many of the molecules and processes identified in *Aplysia*'s learning are also involved in human learning.

The fruit fly *Drosophila* is also commonly used to study behavior, especially how genes control behavior. For example, variations in a gene called 'foraging' determine whether flies tend to roam around as they eat or sit in one place. Flies with mutations in another gene called 'timeless' don't have normal circadian rhythms. Mutations have been identified that affect the full gamut of *Drosophila* behaviors — from aggression to courtship, as well as learning and memory. Many of the affected genes have correlates in humans.

Addiction presents one of the most pressing challenges in studying human behavior — how to better understand it and how to treat it. Some lab animals like rats will consume alcohol and drugs even if accompanied by a bitter taste or foot shock. Scientists have uncovered changes in the brains of animals exhibiting such addiction-like behaviors that mirror changes seen in the brains of humans with addiction disorders. Interestingly, some breeds of rats are very likely to exhibit addiction and relapse behaviors while others are more resistant. By comparing the genetics of two breeds of rats with different predispositions to cocaine addiction, scientists identified genes that were differentially turned on or off in the two breeds; the study suggests that these genes, and their epigenetic regulation, play a role in susceptibility to addiction. This type of research helps scientists understand why some people are more prone to addiction or relapse, and could suggest ways to identify people at risk.



National Human Genome Resource Institute.

Because its nervous system is much simpler than that of a mammal, the sea slug *Aplysia* was an important animal model in early studies on the neurobiology learning and memory.

Paulomelo.adv.

Drosophila melanogaster, pictured here, is widely used for studying many aspects of the brain and behavior.

Behavior is also studied directly in humans. Early mapping of human behaviors to specific brain regions was done by observing personality changes in people who had lost small regions of their brain due to injuries or surgeries. For example, people who have lost their frontal lobe often become inconsiderate and impulsive. Modern imaging techniques, described in greater detail below, also help scientists to pair brain regions with certain behaviors. For example, imaging allows researchers to see certain brain areas "light up" when a person is shown human faces, but not when they see faces of other animals. These techniques are also useful to better understand brain disorders — such as identifying brain regions responsible for auditory hallucinations in schizophrenia.

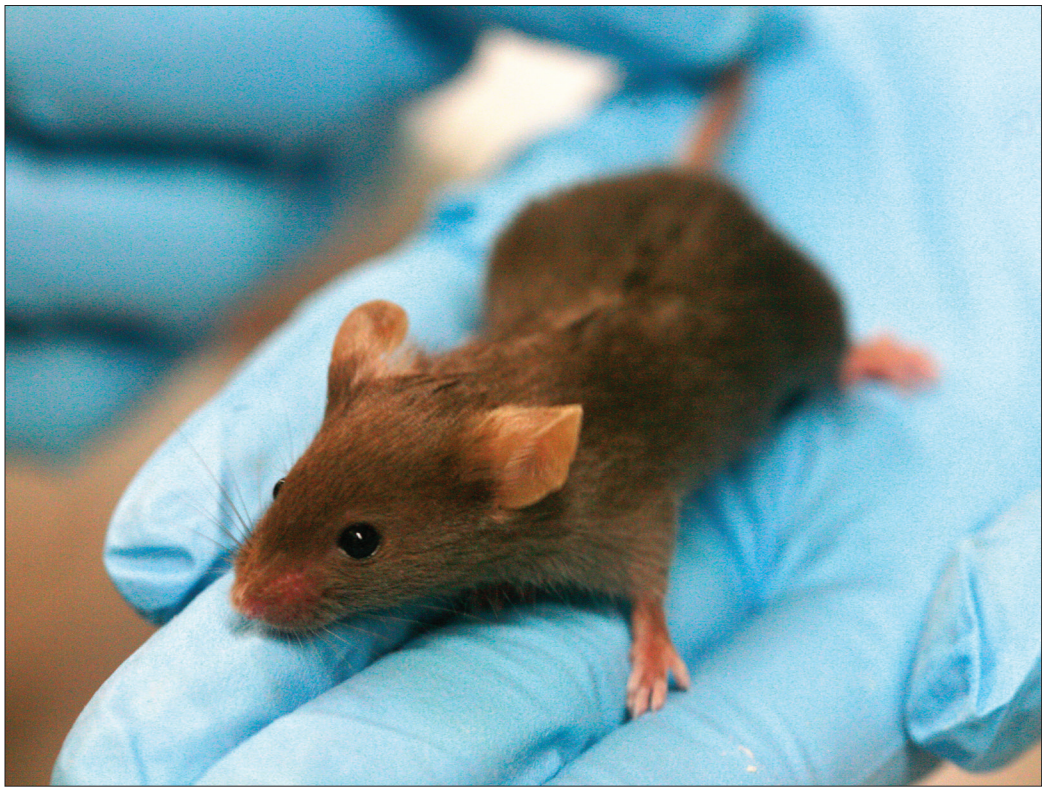
TOOLS FOR BIOCHEMISTRY

Although we talk a lot about the electrical signals transmitted along neurons, the brain also communicates with molecular and chemical signals. Neurotransmitters are chemical messengers that travel *across* a synapse, carrying signals from one neuron to the next. Using a method called microdialysis, researchers can monitor neurotransmitters in action. With thin tubes inserted into the brain, scientists are able to collect tiny volumes of liquid from just outside neurons and then analyze the compounds in that liquid. For example, a researcher could analyze liquid captured during learning to identify molecules that are important for that process.

Microdialysis can also be used to deliver compounds to the brain. Many drugs have powerful effects on the brain, so scientists can use these substances to tweak brain function in order to understand it better.

Pharmacology, the study of the effects of drugs, is also dedicated to identifying new drugs to treat conditions like pain or psychiatric illness, as well as understanding addiction and other negative consequences of drug use.

Another important method employed to study the molecules and chemicals at work in the brain is mass spectrometry. Once a sample has been collected — perhaps by using microdialysis — the compounds it contains are ionized (given an electric charge) and then sent through an electric or magnetic field. The behavior of each molecule in that field indicates its mass. That information alone provides valuable clues for identifying a molecule. Mass spectrometry has also been very useful in exploring neurodegenerative disorders. For example, one treatment for Parkinson's disease causes severe side effects, including involuntary movements. With mass spectrometry, researchers have identified the location within the brain where this side effect is caused; that information could point the way to interventions that can reduce or prevent those side effects.



Rama.

Mice are one of the most important animal models in neuroscience research.

TOOLS USED FOR HUMAN RESEARCH

Many of the methods we have discussed are too invasive to use in humans. But several methods for imaging human brain function do *not* require holes in the skull or other lasting physical changes. Functional MRI (fMRI) can be used to follow changes in the brain activity of a person lying inside an MRI scanner. The machine is tuned so that it detects blood flow as well as differences in oxygen-rich and oxygen-poor blood, based on the idea that more active regions of the brain need more oxygen and nutrients, which

iStock.com/nattrass.

Magnetic resonance imaging (MRI) scans are used to create detailed images of organs like the brain.

are supplied by fresh oxygenated blood. While this is an indirect indication of neuron activity, it can pinpoint brain activity to fairly small regions.

fMRI provides an indirect view of neuron activity, but magnetoencephalography (MEG) detects actual electrical currents coursing through groups of neurons. When neuron activities are synchronized, their combined electrical currents produce weak magnetic fields that MEG equipment can detect. A person undergoing the procedure sits or lies down, with his or her head surrounded by a helmet-shaped device that can sense magnetic fields. MEG has been useful in a variety of studies: from how the auditory cortex responds to sounds to identifying where epileptic seizures start in a patient's brain. MEG is useful for detecting rapid changes in brain activity (temporal resolution) but it does not provide the precise location of that activity (spatial resolution). For this reason, researchers can combine MEG data with fMRI data to obtain good anatomical detail from fMRI and high-speed readings of brain activity from MEG.

Near-infrared spectroscopy (NIRS) is similar to fMRI in that it monitors the flow of oxygenated blood as a way to estimate neuron activity. A major difference is that NIRS is only useful for measuring activity near the surface of the brain and does not provide as much detail; however, it is far less expensive and cumbersome than fMRI. NIRS is also more comfortable for the person undergoing the procedure, as the setup essentially involves wearing a cap with wiring hooked to it. Some of the wires transmit harmless laser beams (~1 megawatt of power or less) into the brain while others detect the light after it travels through the brain. NIRS can be used to determine the extent of brain injuries and to monitor oxygen levels in the brains of patients under anesthesia. Because of its portability, NIRS is very useful for studying brain activity during tasks — such as driving down the highway — that can't take place inside an fMRI scanner.

Positron emission tomography (PET) detects short-lived radioactive compounds that have been injected into the bloodstream. The radioactive compounds could be oxygen or glucose, or they might be a neurotransmitter. PET traces where these compounds go in the body. The location of labeled oxygen can indicate blood flow, while a labeled neurotransmitter can show which brain regions are using that signaling molecule. PET can also detect the amyloid plaques that are a hallmark of Alzheimer's disease; this technique could one day enable us to identify the disease in its early stages. Although PET has good temporal resolution like MEG, it lacks the detailed spatial resolution of MRI.

Some methods used in human research can change brain activity. In transcranial magnetic stimulation (TMS), a coil that generates a magnetic field is placed near a person's head. The magnetic field can penetrate the skull, temporarily activating or silencing a region of the cortex. TMS is used to treat psychiatric disorders such as anxiety, depression, and post-traumatic stress disorder and could be an effective option for patients with conditions that do not respond to medications.

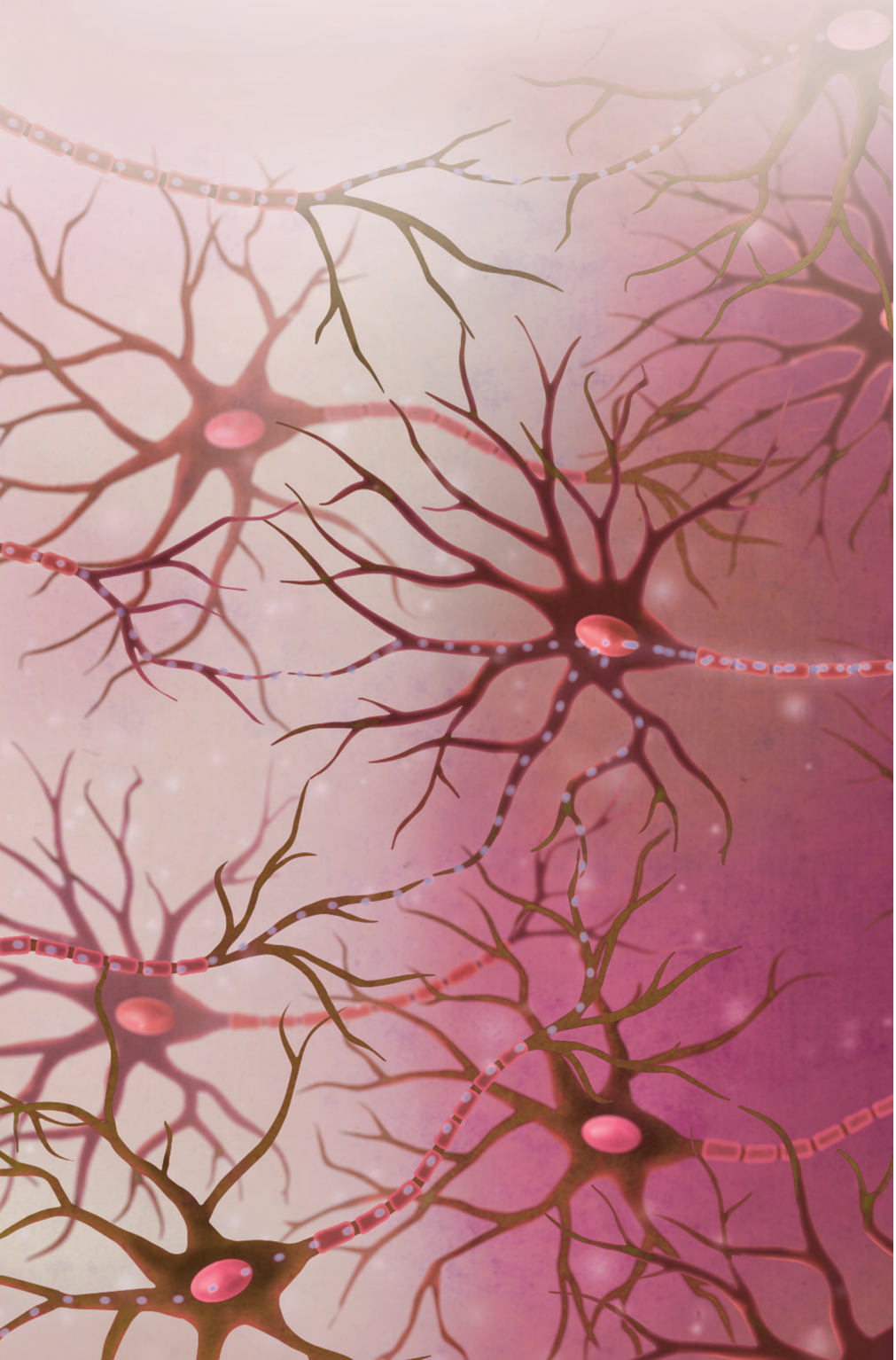
Although neuroscience has progressed by leaps and bounds since neurons were first viewed under a microscope, many phenomena observed with these techniques are not fully understood. For example, mysteries still surround data obtained with EEG. EEG shows that several different brain regions have characteristic rhythms or oscillations — one pattern in the visual cortex, another in the sensory motor cortex, and so on. Even though this method of examining brain activity has been used since 1929, the generation of these patterns (sometimes called brain waves) at the level of neural circuits is not well understood.

One branch of neuroscience that can help bridge findings from the microscopic to the whole-brain level is computational neuroscience. Researchers in this field develop theories or models about how the brain processes information, then test these models against real-world data. For example, they can examine the data and images from EEG or fMRI, then develop mathematical models to explain the underlying neuron and circuit activity. Data from the many methods discussed in this chapter — electrophysiology, molecular studies, anatomy, and functional brain scans — can all contribute to these computational models.

This chapter provides an introduction to research methods that have driven, and continue to drive, discovery in neuroscience. As new techniques and technologies emerge, scientists will add them to their repertoire of techniques that can deepen our understanding of the brain and suggest new ways to help people whose lives are affected by brain disorders.

CHAPTER 17

Solving Human Problems



BRAIN-MACHINE INTERFACE

If you know someone with severe neurological damage — perhaps cerebral palsy, trauma from a car or motorcycle accident, a military or sports injury, or a stroke — you've seen, firsthand, how communicating with the outside world and performing daily tasks can be a challenge. But during the past few decades, scientists have made impressive progress in developing technologies that can bypass such damage. Now brain-machine interfaces can read the activity of millions of neurons — through electroencephalographic (EEG) activity from the brain's surface or from implanted electrodes — and predict the behavioral intentions of research participants. These advances give human and animal subjects neural control of parts of their surroundings: from computer cursors to video games to robotic limbs.

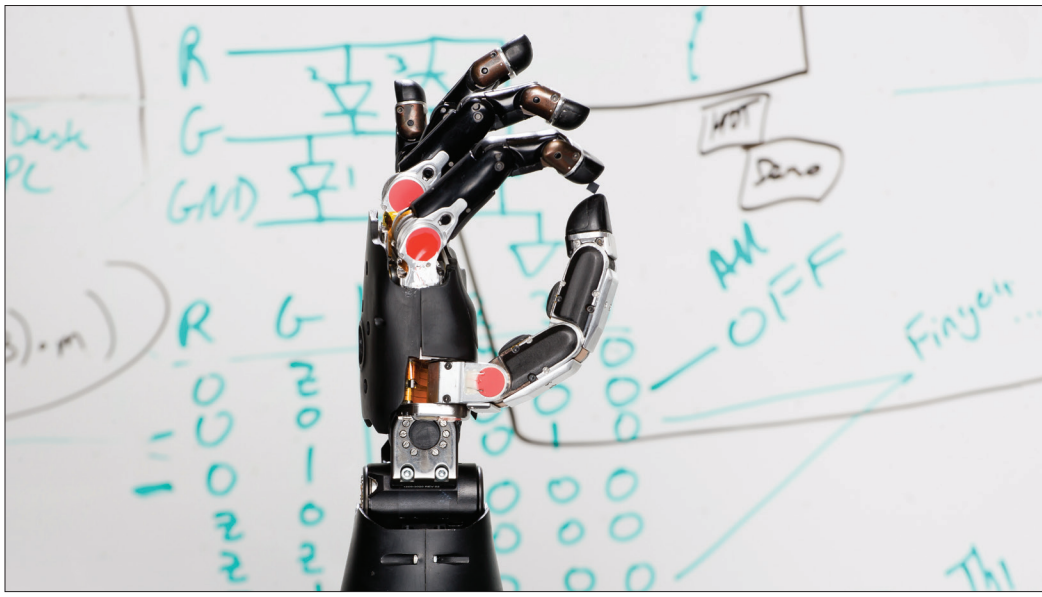
Despite the sci-fi sizzle, most of the work on electronic brain implants is derived from basic research on how animals and people plan and control various types of movement. Using hair-thin wires inserted into the brains of monkeys and rats, scientists first recorded the firing patterns of cells located in the premotor, primary motor, and posterior parietal cortical areas of the brain. As the animals performed repetitive tasks like pressing a lever to receive a reward, researchers found specific firing patterns associated with the motion. Eventually, these patterns were translated into computer algorithms that allowed animals to complete a task via a robotic arm or prosthetic device simply by thinking about it.

The clinical applications of brain-machine interfaces quickly became clear. Neuroscientists and surgeons implanted electrode arrays in the brains of patients with epilepsy, paralysis, stroke,

or Lou Gehrig's disease (ALS), in hopes of enabling them to communicate and, someday, move independently. In early experiments, patients were only able to gain rudimentary control of a computer cursor. But a breakthrough occurred in 2011 when, after months of extensive training, quadriplegic patients learned to control movements of a third (robotic) arm — enabling them to grasp a drink of water or reach out to a loved one.

Honing this technology is allowing patients to control their own paralyzed limbs. Electrode chips implanted in their brains are connected to sleeves or gloves worn over the injured limbs. Sending tiny blasts of electricity into the patient's nerves, located under the sleeve or glove, can reanimate paralyzed muscles. But brain-machine interfaces won't become part of clinical medicine until they're simplified, miniaturized, and made more reliable. Devices that wirelessly transmit commands from brain implants are a step in that direction.

A parallel line of research has explored applying this technology in the broader field of neuroprostheses. Neuroprosthetic devices not only receive output commands from a patient's nervous system, but can also provide input — as occurs in retinal implants and prosthetic limbs. Prosthetic arms, for example, have remained frustratingly low-tech, but some brain-guided prostheses have integrated nerves and muscles at several different levels, allowing users to perform more precise and natural movements, and even enabling some to "feel" again. Still, even the most sophisticated neuroprostheses (such as brain implants) are limited by their number of electrodes and the lifespan of the implanted electrodes. Current arrays can only connect to 100 or so neurons, so a more complex and useful bionic future is still far away. Yet scientists and entrepreneurs



DARPA.

Advances in brain-machine interfaces are leading to incredible treatments, like this prosthetic arm that is controlled through thought.

are already thinking of new uses for the technology: restoring memory; enhancing cognition; and treating diseases such as depression, Alzheimer's, and epilepsy.

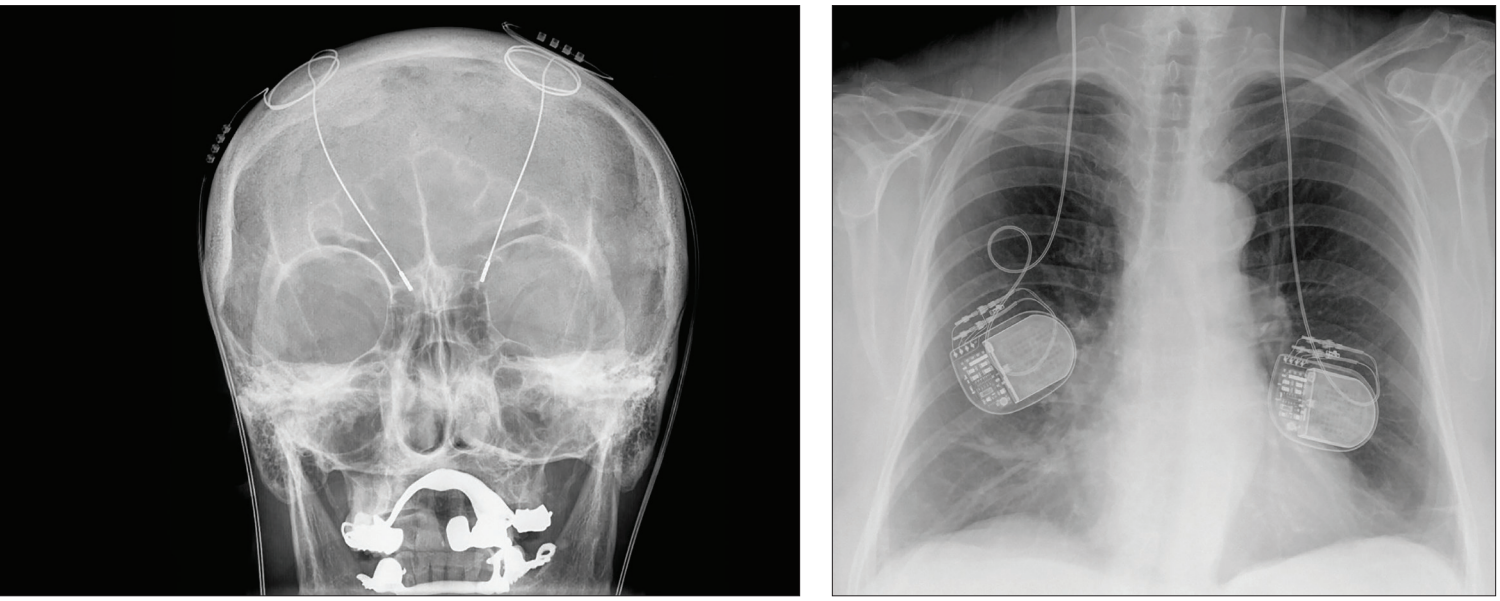
DEEP BRAIN STIMULATION

Insights into the pathophysiology of movement disorders have rekindled interest in the use of focused electrical stimulation as a form of treatment. The most advanced and precise method — deep brain stimulation (DBS) — was inspired by pacemakers engineered for the heart. Instead of electrodes implanted in the heart, the electrodes of the DBS device are surgically embedded in specific brain regions. Depending on where the electrodes are placed, DBS devices can help alleviate the symptoms of some brain disorders.

During most of these implantation surgeries, patients remain awake so that a neurologist can talk to them and ensure that the electrodes are stimulating the correct locations. While the patient's head is held in place with a stereotactic frame, the surgeon drills a dime-sized hole (or smaller) in the skull. Then, a thin insulated wire with electrodes at the tip or along the shaft is inserted deep into the brain; if both sides of the brain are to receive implants, a wire is inserted into each side. In a separate surgery, a battery-operated pulse generator is implanted in the upper chest and connected to the electrodes. When the device is turned on, it starts sending electrical currents that alter the activity of the targeted brain cells.

The implanted device relies on the fact that neuronal communication uses electrical signals. In many movement disorders, an abnormal signal or pulse can gain control of a circuit and can easily become magnified. Like someone shouting in a crowded room, this aberrant signal can drown out other activity. DBS interrupts the shouting, so that normal communication can continue.

To determine where brain activity needs to be silenced or induced, neurosurgeons must identify the locations of the problems. The brain areas first targeted for tremors and Parkinson's disease were chosen after years of painstaking neuroimaging, neuroanatomy,



Hellerhoff.

Deep brain stimulation uses electrodes implanted deep in the brain, which carry electric impulses to specific brain regions. The power packs that provide the electricity are implanted in the patient's back, as seen in this X-ray.

and fundamental research, especially in nonhuman primate models. Since then, deep brain stimulation has been used to treat epilepsy, dystonia, Tourette's syndrome and, more recently, obsessive-compulsive disorder. Now researchers are investigating whether the DBS technique can potentially be extended to mood disorders such as treatment-resistant depression, as well as other complex mental disorders.

Yet DBS, like any surgical procedure, is not without some risks. It is highly invasive, and potential complications include infection, stroke, and bleeding in the brain. It also requires regular neurological follow-up and battery changes every 3 to 4 years.

PSYCHOACTIVE THERAPIES

Transcranial Stimulation

A few noninvasive treatments can stimulate cells near the surface of the brain: Transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS) all use magnetic fields or low electrical currents to alter neural activity in a specific region of the human cortex and, indirectly, deeper brain structures to which it connects.

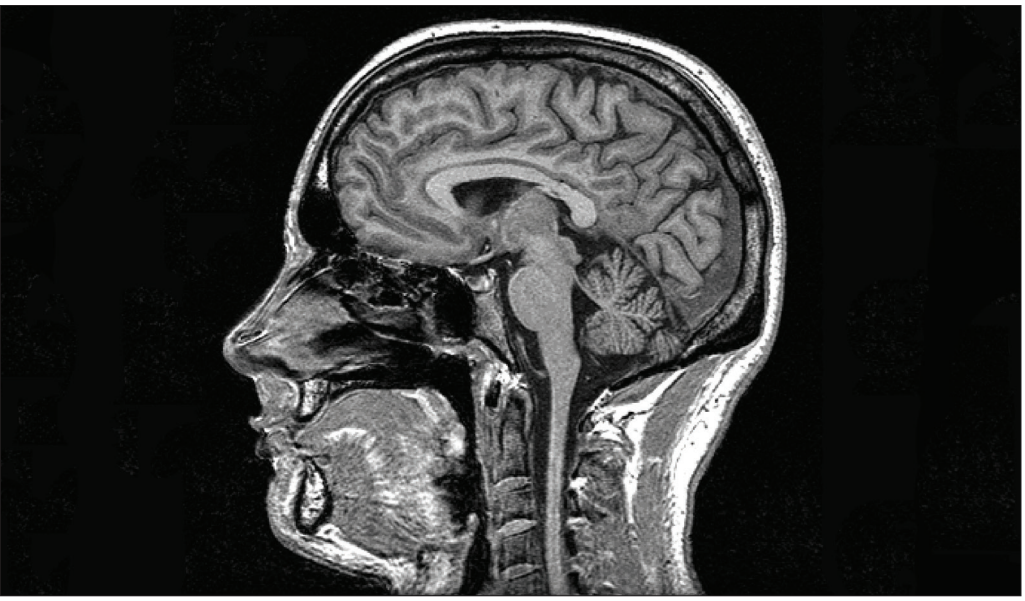
During TMS therapy, patients sit in a chair while a nurse or technician places a magnetic stimulator against their head. The device painlessly delivers brief magnetic pulses to the brain, similar in strength to those generated by magnetic resonance imaging (MRI) devices, but highly targeted. For patients with depression, pulses are focused over their left prefrontal cortex. Here, they generate electrical currents among neurons which, over time, help lift the patient's mood.

Similarly, tDCS uses one or two milliamperes of direct current to tune the brain. Although research into tDCS and its close cousin, tACS, is in its early stages, these techniques offer clear advantages over deep brain stimulation and even over TMS. Generally, patients report only a slight tingling or tapping feeling on their head as the therapy is administered. The devices used to administer these therapies are also cheaper, more portable, and lower-tech compared to TMS and DBS.

A number of studies have suggested that tDCS and tACS might be used to improve working memory as well as to relieve chronic pain and the symptoms of depression, fibromyalgia, schizophrenia, and other disorders. However, despite the substantial literature, meta-analyses have failed to conclusively prove any effects of transcranial electrical stimulation. Currently, there is no consensus among scientists on how these treatments might work, or even on the best way to position the stimulation devices.

New Types of Drugs

Most doctors still recommend medication as the first line of treatment for neurological and psychiatric disorders. The antidepressants, antipsychotics, and other mind-altering medications used today have been tested in extensive clinical trials and remain largely unchanged from their prototypes developed in the 1950s. Each of these classes of drugs is now filled with subsequent generations of closely



Oxford Centre for Functional MRI of the Brain, Oxford University.

MRI scans can provide detailed images of brain tissue. Here, it displays tissue high in water and fat content in white.

related drugs designed to interact more selectively with their targets, producing better therapeutic effects and fewer side effects, in some cases. Nevertheless, these are just slightly improved copies of one another. Truly novel drug candidates are rare, and hard to develop.

One of the biggest challenges in developing new drugs to treat neurological or psychiatric problems is finding molecules that can cross the protective blood-brain barrier — tightly packed endothelial cells lining blood vessels restrict the kinds of molecules that can enter the brain. While this barrier's fortress-like quality is good for normal function, it prevents most drugs delivered by typical means — including pills, patches, injections, or enemas — from having any useful therapeutic effects within the brain. Scientists have had to design extremely tiny molecules or adopt ingenious strategies such as nanoparticles that shuttle in drugs, enzymes that activate molecules after they've "snuck through" the barrier, and antibodies that were specifically engineered for the brain.

Preliminary trials of drugs that use the body's own immune system to confront and clear unwanted proteins from the brain have sparked a great deal of interest, particularly in the Alzheimer's disease community. When mice and monkeys receive a vaccine that contains a major component of amyloid plaques, their immune systems develop antibodies capable of traveling to the brain and "tagging" the amyloid-beta plaques that are the hallmark of Alzheimer's disease. This tagging seems to alert microglial cells in the brain, which head for the plaques and try to remove them. In some experiments, mice bred to develop an Alzheimer's-like disease remembered how to navigate through a Morris water maze, after being vaccinated — indicating that such vaccines might also relieve symptoms of the disease.

In the past, however, many Alzheimer's vaccines have failed in later-stage clinical trials. One reason for these failures was the development of harmful side effects. Several human participants experienced severe inflammation when their brains reacted to the antibodies against its proteins. Since then, newer approaches have engineered antibodies or antibody fragments that bind to their specific targets without triggering an autoimmune response. Other researchers have engineered double-duty antibodies. These use one end to sneak into the brain by binding to a receptor on the blood-brain barrier. Once inside, the antibody's other end can cut off production of harmful amyloid-beta proteins even before plaques form.

By contrast, some therapies aim to boost helpful peptides and proteins called trophic factors, which are native to the brain. Neurotrophic factors support the growth and survival of specific groups of neurons. Scientists hope to modify these factors to reduce the amount of cell death in various neurodegenerative diseases.

The possible value of at least one trophic factor — nerve growth factor (NGF) — has already been demonstrated in several preclinical and early stage clinical trials. NGF slows the destruction of cholinergic neurons that plays a role in the cognitive decline of Alzheimer's disease. Injecting NGF into patients' brains stimulated the regeneration of these neurons and induced sprouting of new nerve fibers around the injection site. In some cases, evidence of this sprouting lasted up to 10 years after the initial therapy.

Brain-derived neurotrophic factor (BDNF) is showing potential for treating Alzheimer's disease, as well as Huntington's, Parkinson's, ALS, and Rett syndrome. Moreover, the effects of boosting BDNF could even be stronger than those of NGF. But, in an interesting twist, the *inhibition* of some neurotrophic factors such as the neurite outgrowth inhibitor might also benefit patients. Studies have

found that neurite outgrowth inhibitor is upregulated in the early stages of motor disease, and having too much of it around could prevent nerve regeneration. Scientists are now conducting clinical trials in which patients with ALS and spinal cord injuries receive custom-made antibodies to disable the neurite outgrowth inhibitor protein.

Ultimately, the ever-increasing global demand for therapies for neurological and mental diseases is a strong motivator for scientists and doctors in this field.

PREDICTIVE NEUROIMAGING AND PERSONALIZED MEDICINE

As we gain understanding of the anatomical and functional changes underlying neurological illnesses, it becomes increasingly clear that these changes provide clues for earlier detection — even before symptoms appear. Many disorders, such as Alzheimer's disease, are accompanied by specific brain activity and structural changes that can be tracked over time using MRI. By comparing this information with a baseline model of a healthy brain, researchers hope to predict which patients might one day develop neurological problems.

Although it is still too early for these "markers" to be used as clinical reference points, they could pave the way for objective diagnoses of brain disorders, much as electrocardiograms and laboratory tests are currently used to reveal heart problems. The first step in this process is to produce a generic brain template by averaging the images from hundreds of randomly selected MRI scans. Scientists can then use machine-learning software to characterize the sets of healthy brain scans and the sets of scans known to show disease-associated changes.

Data from predictive neuroimaging can also be useful for guiding personalized treatment options and assessing a treatment's clinical effectiveness. In studies of major depression, for example, patients whose brain scans showed an overactive amygdala (a brain region involved in emotional processing) were more likely to respond to psychotherapy. However, patients who exhibited higher activity in the anterior insula (another brain region involved in emotions) tended to improve with medication, but not with psychotherapy. In the future, psychiatrists could offer patients the best possible course of treatment based on their own biological characteristics, rather than relying only on symptoms or treatment preferences.

CELLULAR MARKERS

In the past few years, a growing number of clinicians and scientists have rejected the boundaries of conventional DSM (Diagnostic and Statistical Manual of Mental Disorders)-defined diagnostic protocols that mental health professionals usually rely on. Rather than analyzing symptoms such as sadness, fatigue, or lack of sleep, the focus has shifted to finding biological markers that provide objective indices of those symptoms.

Much like neuroimaging, cellular markers could be used to predict a patient's risk and diagnosis before disease symptoms become obvious, as well as indicate how a patient may respond to certain treatments. The markers may be proteins, lipids, hormones, nucleic acids, or other compounds that can be detected in samples of blood, urine, saliva, or cerebrospinal fluid.

Although neuropsychiatric research on biomarkers still lags behind other fields such as oncology, researchers are investigating associations between genetic and cellular mechanisms and various mental disorders. A single biological cause for a mental disorder is hard to pin down — in fact, many skeptics say it is impossible to understand mental illness solely by understanding the brain. Causes of mental disorders are very complex and not easy to decipher. And yet, recent technological advances are enabling scientists to decipher more of the brain's mysteries. Researchers can look deeper into the brain with imaging technology, map the circuits underlying specific mental states, and study how chemical levels change in individual neurons. Biomarkers reflect these physiological conditions, and studying them could lead to better targets for treatments. If chosen carefully, biomarkers might even provide useful ways to compare the effectiveness of treatments between patients, as well as in future clinical trials.

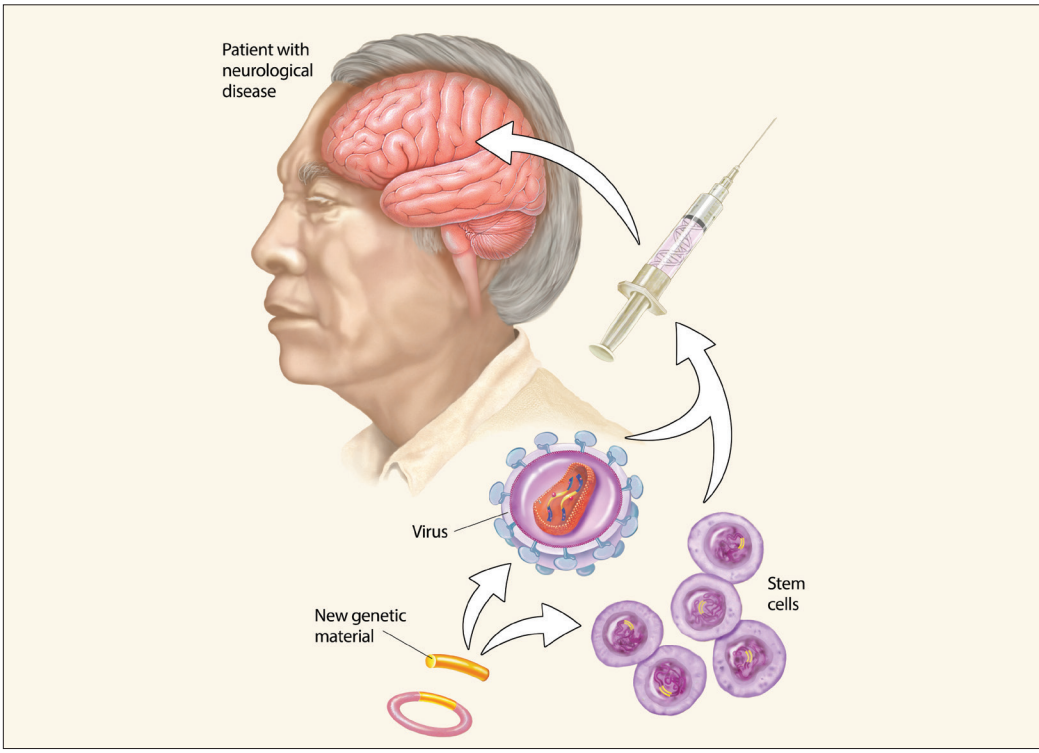
CELL TRANSPLANT

To find new treatments for schizophrenia, stroke, Parkinson's disease and other debilitating diseases, researchers around the world are turning to stem cells to study the biology of the diseases and disorders. These undifferentiated cells — from embryos or from certain adult tissues — have the remarkable potential to develop into any of the three major cell types of the brain: neurons; astrocytes, which nourish and protect neurons; and oligodendrocytes, which surround axons and enable them to conduct signals efficiently. Scientists hope that stem cells transplanted into the brain might be able to replace and repair neural cells that were lost due to disease or injury.

In mice, stem cell therapy has reversed the signs of serious spinal cord injury. Within weeks of treatment, researchers observed that previously

paralyzed mice could walk again. So far, only a few small trials of fetal and stem cell grafts have been conducted in humans. Some of the patients treated showed meaningful recovery from otherwise hard-to-treat disorders like stroke and Parkinson's. Other trials were not successful, with replacement cells starting to produce excessive amounts of dopamine.

Thus, there are several challenges to overcome before successful use of neural stem cell transplant therapy. Embryonic cells and adult stem cells are difficult to harness and transplant into the brain. Controlling where and how stem cells differentiate into the necessary replacement cells is also tricky. Furthermore, stem cells carry a risk of being rejected by the recipient's immune system. Scientists have recently discovered how to convert a patient's own brain cells directly into dopamine neurons, which eliminates many risks, but the procedures are far from standard. None of them has yet been approved by the U.S. Food and Drug Administration.



Stem cell and gene therapies hold huge potential for treating brain diseases. Therapeutic genetic material can be introduced in the brain though engineered viruses, while stem cells can be used to replace damaged or diseased cells in the brain.

GENE REPLACEMENT

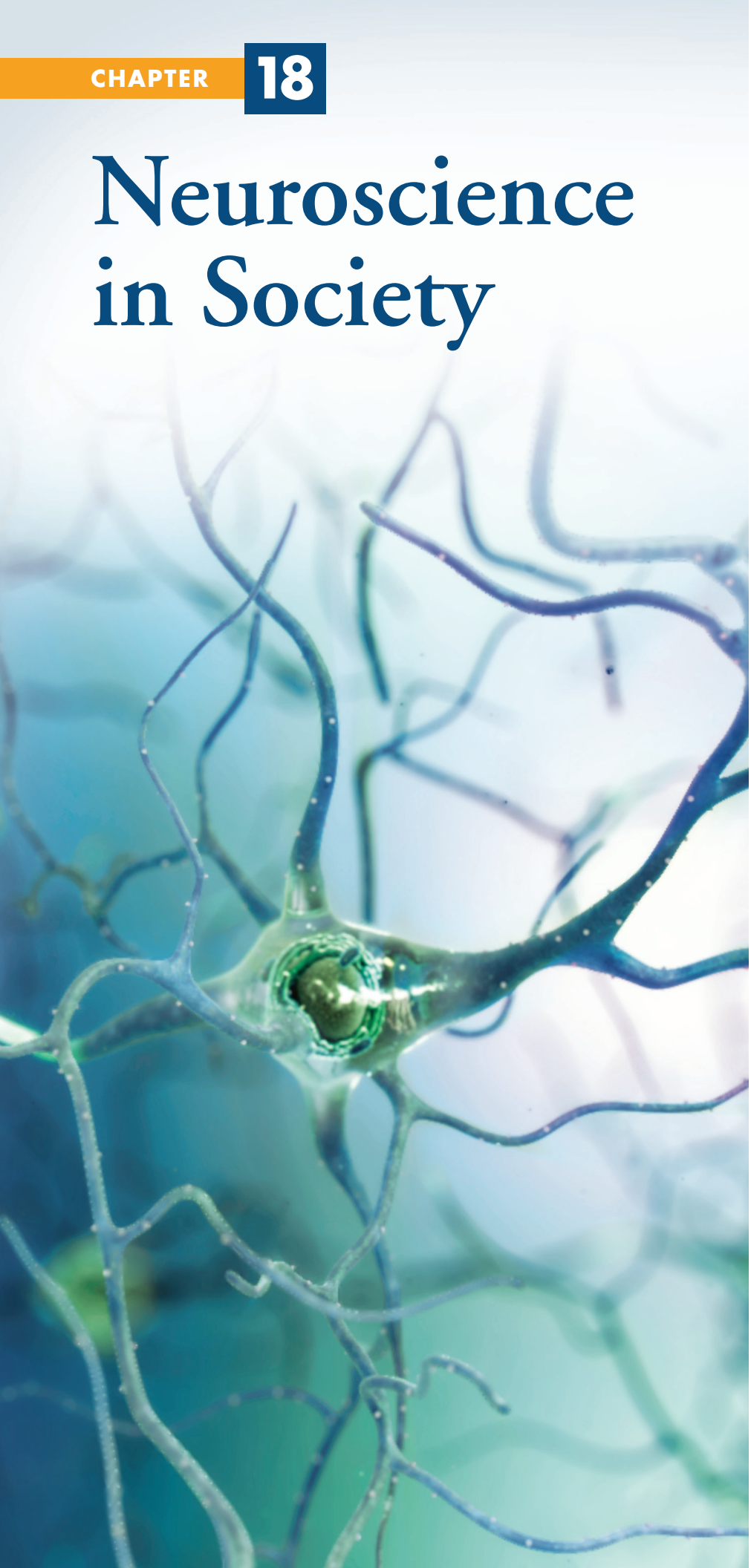
As researchers work to improve the safety and efficacy of genetic and cellular treatments, neuroscientists are finding new ways to deliver therapeutic genes into cells that need them. Designing therapies able to breach the blood-brain barrier is a challenge. Recent research has shown that small viruses with healthy genes tucked inside are able to cross the blood-brain barrier and replace faulty genes. Currently, adeno-associated virus and lentivirus seem to be the safest and most efficient vectors for gene therapy. These vectors are being used in clinical trials in patients with Parkinson's and for some rare genetic diseases. Herpes simplex virus and adenovirus vectors have also been evaluated in early-stage human trials for treating brain tumors.

In recent years, a new gene-editing method, CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), has begun to rewrite "conventional" gene therapy. The new technique uses RNA-guided enzymes to snip out or add DNA segments to a cell, allowing researchers to make extremely precise changes in a cell's genome. Neuroscientists have already used CRISPR to repair part of a gene that produces toxic protein aggregates in the brains of mouse models of Huntington's disease. When scientists looked at the mouse brains a few weeks after the procedure, the aggregated proteins typical of Huntington's were almost gone, and the animals' motor abilities had amazingly improved.

Of course, the usefulness of gene-editing technologies goes far beyond direct therapeutic applications. With CRISPR, dozens of mouse (and other animal) models can be made much more efficiently, facilitating studies of the brain and mental illness. But the technology is still relatively new, and it's not perfect. The CRISPR system can make unintended cuts in the DNA if sequences are similar enough, so that unintended mutations could arise that affect the health of the animal being studied. In addition, this technology is not yet useful for treating complex conditions like schizophrenia and autism, which are thought to involve multiple genes. As with all new technologies, the ethical issues of using CRISPR as a gene therapy in humans are being hotly contested. Only time will tell whether CRISPR can be added to the expanding list of technologies that solve problems of the human brain.

CHAPTER 18

Neuroscience in Society



By this time, you've learned a great deal about your brain and how complicated it is. The preceding chapters have mostly looked at the brain as a part of a thinking, behaving, and feeling individual.

But you rarely live your life as an isolated individual. In fact, you probably interact with a wide variety of people every day, from bus drivers to store clerks to your best friend. Those interactions, along with the interactions of people around you, form the basis of our society. It makes sense that what you've learned about the brains of individuals can help you understand groups of individuals — human societies — and how they function.

Neuroscientists constantly discover new things about the forces that drive the brain. If insights into questions like "How do I make decisions?" or "What causes addiction?" can change one person's life, they can have an even greater influence on groups of people, sometimes even inspiring them to transform the societies in which they live.

Many questions require critical thinking about how the human mind works: "Who decides what the law should be?" "What makes laws fair?" "How can we design the economy, and what groups of people does it leave behind?" Answering these questions requires a thoughtful understanding of the workings of the human mind. Neuroscience can provide evidence-based arguments for how to build a society, rooted in a solid understanding of brain science.

It might sound like science fiction, but the more we discover about the brain, the greater its potential to transform human society. Scientists need to grapple with the ethical dimensions of their work, engaging in conversations with sociologists, lawyers, politicians,

economists, and philosophers to determine the best ways to build on their groundbreaking revelations about the human brain.

NEUROLAW

In earlier chapters, you learned all about decision-making, but many decisions have more drastic consequences than whether to buy a taco or stir fry for lunch. Behind every crime that makes the news is a decision — or a series of decisions — that may have individuals facing the legal consequences of breaking the law. As with so many things (including the brain), the more closely you look at this issue, the more complicated it gets.

Take addiction, for example. In the last few decades, the American prison population has grown by about 500 percent, largely because of drug-related arrests. In this book, you've learned how drug use affects the brain and is associated with significant changes to the prefrontal cortex (PFC), a part of the brain that oversees impulse control and suppressing cravings. Those changes in the PFC make resisting drug use much more difficult. Seen this way, ongoing drug use looks less like a bad decision and more like a symptom of a disease: addiction.

Now lawyers, judges, and scientists have to decide how drug users should be treated by the criminal justice system. Should they continue to be jailed, as a punishment for their decision to break the law? Or should they receive therapy or rehabilitation to treat, and help them recover from their altered brain states? Or should they receive some combination of both? What is the perfect balance?

Many examples muddy the waters of decision-making and punishment. In one famous case, an individual who had brain surgery to remove a tumor suddenly developed a compulsion to view child pornography. During his trial, the man's doctor provided evidence that the surgery had damaged a part of the brain that typically suppresses such dark urges. Personality changes after brain surgeries are not uncommon — was it possible that his terrible fixation was a side effect of his life-saving surgery? If so, what should his punishment be? If the behavior wasn't his "fault," what does a just society owe his victims?

These are not easy questions to answer. They require us to temper our notions of fairness and justice with new scientific knowledge. The more neuroscience reveals to us about the mechanisms underlying memory, personal responsibility, and behavior, the more we must accommodate our social structure to the ramifications of these new discoveries.

For another example, consider eyewitness testimony, a common tool in the courtroom. Studies have found that the testimony of people who actually witnessed a crime is very convincing to juries — more convincing than many types of forensic evidence. But recent research has shown that human memory is far from perfect, especially as time passes after a crime. As witnesses recall their memories, they introduce errors, which are then reconsolidated into new memories. This is true of even the most memorable events. In a study of New York City residents one year after the 9/11 terrorist attacks, their memories of the event differed in 40 percent of the details. This doesn't mean that eyewitness testimony is useless, but neuroscience has demonstrated that it is far from infallible. Judges and lawyers must now come to terms with this change of perspective.

The more neuroscience reveals to us, the more we must accommodate our social structure to the ramifications of these new discoveries.

Nor is this the first time that neuroscience has helped to change the way the courts work. Polygraph tests, once a staple of television crime dramas, have been rejected in many courts (including the United States Supreme Court) as being unreliable. This decision was based on the work of many scientists, who showed that the physiological reactions measured by polygraph tests (sweating, increased heart rate, etc.) are *not* definitively linked to guilt or lying.

After all, dragging an innocent person to the police station to submit to a lie detector test might produce the same symptoms. Reliable lie detection technology might exist one day, but that day is too far in the future to affect current court decisions.

NEUROECONOMICS

You are constantly making financial decisions for yourself. Should you stock up on all of your favorite snacks now that you are at the grocery store, or come back later for the items when there is a big sale? Are you saving enough for college? Do you like that new sports car enough to put up with its poor gas mileage? In recent years, economists and neuroscientists have begun collaborating to investigate the brain processes behind these decisions. This field, called "neuroeconomics," has the potential to significantly alter the way people think about the economy.

A driving force behind modern capitalism is the belief that individuals make rational purchasing decisions — that everyone acting in their own self-interest creates a system in which resources will be distributed as fairly as possible. Yet that theory doesn't explain why so many economic decisions are irrational, or based on gut instinct and rationalized later. Neuroeconomics is especially interested in those situations where choices are less clear-cut or rational and involve unknown (or unacknowledged) factors and risk.

To learn more about these decisions, scientists have measured brain activity as people complete economic tasks — for example, running brain scans as people play a simple double-or-nothing game. When a player decides to risk it all to double winnings, activity increases in a part of the brain called the insular cortex. Scientists hypothesize that networks of the insular cortex interact with other brain areas, including parts of the limbic system that function in learning, memory and emotion, to let the player picture the negative consequences of taking such a risk. Suddenly risking a mortgage payment at the blackjack table might not look so appealing.

Scientists have also discovered that our hormones play a role in economic decisions. In one case, some participants in an investment game were given a dose of oxytocin, a hormone long associated with social bonding. Those who received the oxytocin boost were more trusting with their money and invested larger amounts with a broker. However, if they made investments through a computer program rather than a person, the oxytocin had no effect on their investment strategy. These results suggest that social and neurobiological factors interact to play a role in such decisions, and these kinds of effects are at the heart of many economic decisions. More research in this area could lead to more rational investment strategies.

Another study of male stock traders looked at levels of the hormones testosterone and cortisol. Researchers took saliva samples from a small group of traders every day during a work week, before and after the bulk of their work was done. On days when the traders had higher testosterone levels than average, they took larger risks. However, higher-than-average levels of cortisol (a hormone associated with stress) correlated with risk-averse behavior. With millions of dollars on the line, hormones could be making the difference between a good day at the market and a very bad one.

Research into reward pathways and the way your brain promotes impulsive behavior can help prevent making purchases and decisions that you would regret.

Neuroscience can change our current thoughts about the economy in many other ways. Research on autism spectrum disorders is discovering promising treatments, but also revealing opportunities for workplaces to employ the unique abilities of neurodiverse people. Research into reward pathways and the way your brain promotes impulsive behavior can help prevent making purchases and decisions that you would regret. Scientists are also studying unconscious biases and discrimination, in an effort to help eliminate negative prejudices in hiring

and employment. These are only a few of the practical applications of neuroscience, and more are anticipated. Sometime in the near future, neuroscience could have all the tools needed to design a better, and more inclusive, economic system.

ETHICS AND THE FUTURE OF NEUROSCIENCE

Modern science has the potential to change some of the most fundamental beliefs of our society. Brain science, in particular, has raised many ethical issues. Consider the history of brain research, where early attempts to understand the brain started or exacerbated practices such as phrenology, eugenics, forced sterilization, and unnecessary lobotomies. When the ethical frameworks of science fail, it can incur consequences that affect not only individuals, but society as a whole.

In the future, new technologies that are already on the horizon will raise serious ethical questions. Genetics is one area under intense scrutiny. As you've read in this book, you've seen that many brain diseases have their roots in your genetic code, and scientists are now able to screen for some of these diseases while children are in the womb. Emerging technologies might soon help us identify potential problems and alter a child's genes to prevent it. But is it ethical to alter an unborn child's genetics to cure autism? Other genetic diseases, like Huntington's, will only manifest much later in life. Is it acceptable to "pre-treat" this disease with genetic alterations? What about making children smarter or increasing their chance of getting a perfect math score on their SATs? Some people believe that all children have the right to be genetically enhanced, while others insist that they retain the right *not* to be enhanced.

And who would have access to these enhancements? Will they only be available to children of the rich and powerful, leaving most of us behind? Similar questions can be asked of other therapies, like drugs or devices like transcranial stimulation, which alter the brain in order to treat it.

In the past, these questions were often posed by authors of science fiction. But with the startling technological advances of recent decades, these real-world challenges might be closer than you think. In fact, many scientists and doctors already deal with serious ethical quandaries created by neuroscience. For example, scientists can detect specific biomarkers for disorders such as depression, psychosis, and certain types of chronic pain. Are medical professionals obligated to take steps to treat a disease or disorder that currently shows no symptoms and might never actually materialize? When is the right time to intervene?

There are even thornier questions to consider: When getting permission to treat the brain in some way, the organ that gives consent is the same as the organ being treated. How does that affect the idea of "informed consent" in cases like Alzheimer's disease or a debilitating brain tumor? Should a doctor proceed with treatment when the patient (that is, his or her brain) might not have had the ability to properly consent?

The questions raised in this chapter have no easy answers. Your responses could depend on your religion, your socioeconomic class — and, yes, on the activity of your hormones, your neurotransmitters, and the progressive maturation and aging of your nervous system. The brain is the most complicated structure in the known universe, and investigating its mysteries seems to produce as many questions as answers — and these questions are scientific, ethical, legal and social. But the progress of science has always stirred up "inconvenient" questions about ethical behavior, social conventions, and the proper use of our institutions. Asking those questions early will help researchers and the public work together to create strong ethical frameworks for our evolving society.

Science is an ongoing process. Neuroscience has made many beneficial advances, but facts are also evolving as discoveries emerge. We are only on the very cusp of understanding the billions of cells and trillions of connections that form the human brain. Stay curious about the neuroscience you read in the news, keeping in mind what you have learned in this book to give you context behind the headlines. You are part of science, too. Dialogues between scientists are as vital as dialogues between neuroscientists and society. Creating a forum for debate and discussion holds out the best hope of answering questions in ways that advance our society now and in the future.

Glossary

Acetylcholine A critical neurotransmitter that controls functions such as memory, attention, sleep, heart rate, and muscular activity.

Action Potential An electrical charge that travels along the axon to the neuron's terminal, where it triggers the release of a neurotransmitter. This occurs when a neuron is activated and temporarily reverses the electrical state of its interior membrane from negative to positive.

Addiction Loss of control over drug intake or compulsive seeking and taking of drugs, despite adverse consequences.

Adenosine A neurochemical that inhibits wakefulness, serving the purpose of slowing down cellular activity and diminishing arousal. Adenosine levels decrease during sleep.

Adrenal Gland An endocrine organ that secretes hormones. The outer layer (adrenal cortex) secretes the stress hormone cortisol. The inner portion (adrenal medulla) secretes epinephrine and norepinephrine in concert with the activation of the sympathetic nervous system in the "fight or flight" response.

Alzheimer's Disease (AD) A major cause of dementia in the elderly, this neurodegenerative disorder is characterized by the death of neurons in the hippocampus, cerebral cortex, and other brain regions. The earliest symptoms of the disease include forgetfulness; disorientation as to time or place; and difficulty with concentration, calculation, language, and judgment. In the final stages, individuals are incapable of self-care and may be bedridden.

Amnesia A memory impairment usually caused by brain damage or disease, or by drugs such as some anesthetics. People with amnesia may be unable to recall events from the past, form new memories, or both.

Amygdala A structure in the forebrain that is an important component of the limbic system and plays a central role in emotional learning, particularly within the context of fear.

Amyotrophic Lateral Sclerosis (ALS) Commonly known as Lou Gehrig's disease, ALS causes motor neurons in the brain and spinal cord to disintegrate, resulting in loss of control of voluntary muscle movements such as walking.

Analgesic A drug that relieves pain without causing a loss of consciousness.

Anxiety A state of heightened arousal characterized by intense worry.

Aphasia Disturbance in language comprehension or production, often as a result of a stroke.

Apoptosis Programmed cell death induced by specialized biochemical pathways, often serving a specific purpose in the development of an animal.

Arousal A physiological state involving changes in the body and brain that motivate behavior and enable response to stimuli.

Astrocyte A star-shaped glial cell in the central nervous system that nourishes neurons; regulates the formation, maintenance, and pruning of synapses; and contributes to the blood-brain barrier.

Attention A state of arousal in which the brain's sensory processing is directed at a limited number of stimuli. Voluntary (endogenous) attention is a conscious decision to focus on a particular stimulus. Involuntary (exogenous) attention is an unplanned focus on a change in the environment, such as a loud noise or sudden movement.

Attention Deficit Hyperactivity Disorder (ADHD) A condition characterized by excessively inattentive, hyperactive, or impulsive behaviors.

Auditory Nerve A branch of the vestibulocochlear nerve that transmits auditory information from the cochlea of the ear to the brain.

Autism Spectrum Disorder (ASD) A set of conditions characterized, in part, by impaired social communication and interaction, and narrow, obsessive interests or repetitive behaviors.

Autonomic Nervous System A part of the peripheral nervous system responsible for regulating the activity of internal organs. It includes the sympathetic and parasympathetic nervous systems.

Axon The fiber-like extension of a neuron by which it sends information to target cells.

Axon Terminal The ends of axons where neurotransmitters are released to target cells.

Basal Ganglia A group of interconnected structures located deep in the brain that play an important role in voluntary movement, motor skill learning, and habits. These structures include the caudate nucleus, putamen, nucleus accumbens, globus pallidus, and substantia nigra.

Benzodiazepines A class of drugs that enhance activity of the brain's primary inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), to produce sedative and anti-anxiety effects. Benzodiazepines are often prescribed to treat anxiety disorders and insomnia.

Blood-Brain Barrier A protective membrane composed of tightly packed endothelial cells lining the brain's capillaries and highly specialized astrocytes, which controls the passage of certain molecules into and out of the brain.

Brain Waves Oscillating patterns of brain activity that can be detected and recorded using electroencephalography (EEG).

Brain-Derived Neurotrophic Factor (BDNF) A neurotrophic peptide that supports the growth and survival of neurons.

Brainstem The major route by which the forebrain sends information to and receives information from the spinal cord and peripheral nerves. The brainstem includes the midbrain, pons, and medulla, and it controls, among other things, respiration and the regulation of heart rhythms.

Broca's Area A region of the frontal lobe — usually the left hemisphere — that governs speech production.

Cell Body Also called the soma, the part of a neuron that contains the nucleus (with DNA) and the organelles, but not the projections such as the axon or dendrites.

Central Nervous System The brain and spinal cord.

Cerebellum A large structure located at the roof of the hindbrain that helps to control the coordination of movement by making connections to the pons, medulla, spinal cord, and thalamus. It also may be involved in aspects of motor learning.

Cerebral Cortex The wrinkled, outermost layer of the cerebrum consisting primarily of neuron cell bodies.

Cerebrum The largest part of the human brain associated with higher order functioning, such as thinking, perceiving, planning, and understanding language, as well as the control of voluntary behavior.

Circadian Rhythms A cycle of behavior or physiological change lasting approximately 24 hours.

Cochlea A snail-shaped, fluid-filled organ of the inner ear responsible for converting sound into electrical potentials to produce an auditory sensation.

Cognitive Behavioral Therapy A form of counseling used to identify and change negative thought patterns that can contribute to anxiety and mood disorders.

Computational Neuroscience A field of neuroscience research that uses computer programs and algorithms to analyze information about the brain, and develops mathematical models to explain brain function.

Cones A primary receptor cell for vision located in the retina. It is sensitive to color and is used primarily for daytime vision.

Corpus Callosum The large bundle of nerve fibers linking the left and right cerebral hemispheres.

Cortisol A hormone manufactured by the adrenal cortex. In humans, cortisol is secreted in the greatest quantities before dawn, readying the body for the activities of the coming day.

Cranial Nerves Twelve pairs of nerves that can be seen on the bottom surface of the brain. Some of these nerves transmit sensory information; some control the movement of face, head, and neck muscles; others transmit information to internal organs to regulate functions such as blood pressure and heart rate.

Critical Period A period of heightened plasticity in brain development when certain experiences and sensory inputs are required for the formation of functional brain circuits.

Declarative Memory Also called explicit memory, a type of memory that can be consciously retrieved. It includes memory of facts (semantic memory) and memory of personal experiences (episodic memory).

Default Mode Network A collection of brain regions activated during quiet rest.

Dementia A decline in cognitive ability that interferes with day-to-day functioning.

Dendrite A treelike extension of the neuron cell body. The dendrite is the primary site for receiving and integrating information from other neurons.

Depolarization A change in a neuron's membrane potential in which the cytoplasm becomes more positively charged. Neurons must depolarize beyond a certain threshold to generate an action potential.

Depression A psychiatric disorder characterized by sadness, hopelessness, pessimism, loss of interest in life, reduced emotional well-being, and abnormalities in sleep, appetite, and energy level.

Dopamine A catecholamine neurotransmitter present in three circuits of the brain: one that regulates movement; a second, thought to be important for cognition and emotion; and a third that regulates the endocrine system. Deficits of dopamine in the motor circuit are associated with Parkinson's disease. Abnormalities in the second circuit have been implicated in schizophrenia.

Down Syndrome A condition that results from the presence of an extra copy of chromosome 21. This genetic anomaly is associated with physical and developmental characteristics, including mild to moderate intellectual disabilities; low muscle tone; and an increased risk of congenital heart defects, respiratory problems, and digestive tract obstruction.

Dyslexia A pronounced difficulty with reading despite normal intelligence, education, and motivation.

Electroencephalography (EEG) A technology used to record electrical activity of the human brain in response to a variety of stimuli and activities.

Endorphins Neurotransmitters produced in the brain that generate cellular and behavioral effects like those of morphine.

Epilepsy A disorder characterized by repeated seizures, which are caused by abnormal excitation of large groups of neurons in various brain regions. Epilepsy can be treated with many types of anticonvulsant medications.

Epinephrine A hormone released by the adrenal medulla and specialized sites in the brain. During times of stress, epinephrine, also known as adrenaline, is quickly released into the bloodstream. It then serves to put the body into a general state of arousal, which enables it to cope with the challenge.

Episodic Memory A type of declarative memory consisting primarily of memory of personal experiences.

Estrogen A female sex hormone produced primarily in the ovaries.

Excitation A change in the electrical state of a neuron that is associated with an enhanced probability of action potentials.

Excitatory A type of neuron (or neurotransmitter) that excites target neurons and increases the likelihood of their firing an action potential.

Executive Function Higher-level processing that takes place in the brain's prefrontal cortex. Executive function comprises impulse control, working memory, and mental flexibility.

Forebrain A region of the developing brain that goes on to become the cerebral hemispheres and major parts of the limbic system.

Fovea A small, pitted area in the center of the retina where visual acuity is highest, due to a high density of cones.

Fragile X Syndrome A genetic condition resulting from a mutation in the FMR1 gene that causes intellectual disability.

Frontal Lobe One of the four subdivisions of the cerebral cortex. The frontal lobe has a role in controlling movement and in the planning and coordinating of behavior.

Functional Magnetic Resonance Imaging (fMRI) A technology that uses magnetic fields to detect activity in the brain by monitoring blood flow.

Gamma-Aminobutyric Acid (GABA) An amino acid neurotransmitter in the brain whose primary function is to inhibit the firing of nerve cells.

Glia Specialized cells that nourish and support neurons.

Glucocorticoid Hormones Hormones that produce an array of effects in response to stress. Some of the actions of glucocorticoids help to mediate the stress response, while other, slower actions counteract the primary response to stress and help to re-establish homeostasis.

Glutamate An amino acid neurotransmitter that acts to excite neurons. Glutamate stimulates N-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA). AMPA receptors have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in developing animals. Stimulation of NMDA receptors may promote beneficial changes, whereas overstimulation may be a cause of nerve cell damage or death in neurological trauma and stroke.

Gray Matter Portions of the brain that are gray in color because they are composed mainly of neural cell bodies, rather than myelinated nerve fibers, which are white. It includes the cerebral cortex as well as s ubcortical structures.

Growth Cone A distinctive structure at the growing end of most axons. It is the site where new material is added to the axon.

Hair Cells Sensory receptors in the cochlea that convert mechanical vibrations to electrical signals; they in turn excite the 30,000 fibers of the auditory nerve that carry the signals to the brainstem.

Hindbrain The most posterior part of the brain, comprising the pons, medulla, and cerebellum.

Hippocampus A seahorse-shaped structure located within the brain and considered an important part of the limbic system. One of the most studied areas of the brain, it is involved in learning, memory, and emotion.

Histamine A compound with multiple functions in the body. In the brain, histamine acts as a neurotransmitter to stimulate arousal. Local inflammatory responses in the body trigger the release of histamines from immune cells.

Homeostasis The normal equilibrium of body function.

Hormones Chemical messengers secreted by endocrine glands to regulate the activity of target cells. They play a role in sexual development, calcium and bone metabolism, growth, and many other activities.

Huntington's Disease A genetic disorder characterized by involuntary jerking movements of the limbs, torso, and facial muscles, often accompanied by mood swings, depression, irritability, slurred speech, and clumsiness.

Hyperpolarization A change in a neuron's membrane potential in which the cytoplasm becomes more negatively charged and therefore less likely to fire an action potential.

Hypothalamus A complex brain structure composed of many nuclei with various functions, including regulating the activities of internal organs, monitoring information from the autonomic nervous system, controlling the pituitary gland, and regulating sleep and appetite.

Inhibition A change in the electrical state of a neuron that is associated with a decreased probability of firing an action potential.

Inhibitory A type of neuron (or neurotransmitter) that prevents a target neuron from firing.

Insomnia A sleep disorder in which people have trouble falling and/or staying asleep.

Interneuron A neuron that exclusively signals another neuron.

Involuntary Movement A movement that occurs without conscious control, such as a reflex.

Ion Channel Proteins embedded in the cell membrane that allow ions or other small molecules to enter or leave the cell.

Limbic System A group of structures deep within the brain involved in motivation and emotion. The hippocampus, amygdala, thalamus, and hypothalamus are all a part of the limbic system.

Long-Term Memory The final phase of memory, in which information storage may last from hours to a lifetime.

Long-Term Potentiation (LTP) A long-lasting increase in synaptic strength resulting from an increased number of neurotransmitter receptors on the post-synaptic neuron.

Magnetic Resonance Imaging (MRI) A technique that uses magnetic fields to create a high-quality, three-dimensional image of organs and structures inside the body. This technology is noninvasive and does not expose the body to X-rays or other radiation.

Magnetoencephalography (MEG) A technique that can quantitatively measure the strength of activity in various regions of the brain at millisecond resolution.

Medulla Also called the medulla oblongata, a structure of the brainstem that controls basic functions like swallowing, breathing, and heart rate.

Melatonin A hormone produced in the pineal gland that regulates responses to light-dark cycles and induces sleep at night.

Membrane Potential The voltage difference between the inside and outside of a neuron. The typical membrane potential of a neuron at rest is -70mV.

Mentalization The ability to understand the mental states and thoughts of others and oneself.

Microglia Glial cells in the central nervous system that function as resident immune cells.

Midbrain The most anterior segment of the brainstem. With the pons and medulla, the midbrain is involved in many functions, including regulation of heart rate, respiration, pain perception, and movement.

Migration The process whereby new neurons find their proper position in the brain.

Mitochondria Small cylindrical organelles inside cells that provide energy for the cell by converting sugar and oxygen into special energy molecules, called adenosine triphosphate (ATP).

Mood A general state of mind and emotional disposition.

Motor Cortex A specialized region in the cortex involved in the planning and execution of movement.

Motor Neuron A neuron that carries information from the central nervous system to muscles.

Motor Unit A functional unit made up of an alpha motor neuron and all of the muscle fibers it contains and controls, ranging from a few to a hundred or more.

Myelin Compact fatty material that surrounds and insulates the axons of some neurons and accelerates the transmission of electrical signals.

Narcolepsy A sleep disorder resulting from the loss of orexin neurons in the hypothalamus that causes pronounced sleepiness during the day.

Nerve Growth Factor (NGF) A substance whose role is to guide neuronal growth during embryonic development, especially in the peripheral nervous system. Nerve growth factor also probably helps to sustain neurons in adults.

Neurodegeneration The progressive destruction and loss of neurons. Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS) are examples of neurodegenerative diseases.

Neurogenesis The production and growth of new nerve cells during development and, in select brain regions, throughout life.

Neuromodulator A chemical messenger that alters the strength of a synapse by modifying the production and/or response to neurotransmitters. Neurotransmitters, hormones, and immune molecules can all function as neuromodulators.

Neuron A nerve cell specialized for the transmission of information and characterized by long, fibrous projections called axons and shorter, branchlike projections called dendrites.

Neurotransmitters Chemical messengers released by neurons at a synapse for the purpose of relaying information to other cells.

Neurotransmitter Receptors Proteins embedded in the postsynaptic cell membrane that bind neurotransmitters to alter the cell's excitability.

Nociceptors Nerve endings that signal the sensation of pain.

Nodes of Ranvier Unmyelinated gaps in an axon's myelin sheath along which electrical impulses travel.

Nondeclarative Memory Also called implicit or procedural memory, a type of long-term memory that is stored and retrieved without conscious effort.

Norepinephrine A catecholamine neurotransmitter produced both in the brain and in the peripheral nervous system. Norepinephrine is involved in arousal and sleep regulation, mood, and blood pressure.

Nucleus Accumbens A region at the base of the forebrain that is a part of the basal ganglia and is important in motivation and reward.

Obsessive-compulsive Disorder An anxiety disorder characterized by uncontrollable, recurring thoughts (obsessions) and repetitive behaviors (compulsions) that attempt to mitigate the obsessions.

Occipital Lobes One of the four subdivisions of the cerebral cortex. The occipital lobe plays a role in processing visual information.

Olfactory Bulbs Round, knoblike structures of the brain responsible for processing the sense of smell. Specialized olfactory receptor cells are located in a small patch of mucous membrane lining the roof of the nose. Axons of these sensory cells pass through perforations in the overlying bone and enter two elongated olfactory bulbs lying on top of the bone.

Oligodendrocyte A type of glial cell in the central nervous system that forms myelin.

Opioids Substances that bind to opioid receptors in the brain to relieve pain. Endorphins are a type of endogenous opioid produced in the brain. Natural and synthetic opioids, such as morphine and codeine, can be prescribed to treat pain.

Optic Chiasm The place in the brain where the optic nerves meet and some axons cross over to the opposite (contralateral) hemisphere in animals with binocular vision.

Optic Nerve The bundle of neurons that transmit information from the retina to the brain.

Orexin A hormone produced in the hypothalamus that stimulates arousal.

Oxytocin A hormone produced in the hypothalamus and released by the pituitary gland that initiates the release of milk from mammary glands and stimulates uterine contractions. It is also involved in love and social bonding.

Pain An unpleasant sensory and emotional experience often signaling tissue damage, or the potential for damage.

Paralysis The loss of muscle function in all or part of the body, usually due to nerve damage.

Parasympathetic Branch A branch of the autonomic nervous system concerned with the conservation of the body's energy and resources during relaxed states.

Parietal Lobes One of the four subdivisions of the cerebral cortex. The parietal lobe plays a role in sensory processes, attention, and language.

Parkinson's Disease (PD) A movement disorder caused by the death of dopamine neurons in the substantia nigra, located in the midbrain. Symptoms include slowness of movement, muscular rigidity, and walking and balance impairment.

Peripheral Nervous System The nerves outside of the brain and spinal cord.

Photoreceptors A nerve ending, cell, or group of cells specialized to sense or receive light.

Pineal Gland A small endocrine gland in the brain that produces melatonin.

Pituitary Gland An endocrine organ closely linked with the hypothalamus. In humans, the pituitary gland is composed of two lobes and secretes several different hormones that regulate the activity of other endocrine organs throughout the body.

Plasticity The ability of the brain to modify its neural connections to adapt to challenges in the environment.

Pons A part of the hindbrain that, with other brain structures, controls respiration and regulates heart rhythms. The pons is a major route by which the forebrain sends information to and receives information from the spinal cord and peripheral nervous system.

Positron Emission Tomography (PET) A method of measuring brain function based on the detection of radioactivity emitted when positrons, positively charged particles, undergo radioactive decay in the brain. Computers then build three-dimensional images of changes in blood flow based on the amount of radiation emitted in different brain regions. The more brain activity, the more vivid the picture that is created.

Postsynaptic Neuron In a synapse, the neuron receiving chemical messages.

Prefrontal Cortex (PFC) A region at the front of the frontal lobe involved in the brain's higher-level functions such as planning, decision-making, working memory, and inhibitory control.

Presynaptic Neuron In a synapse, the neuron transmitting chemical messages to a target neuron.

Prostaglandins Small lipid molecules that enhance nociceptor sensitivity to increase pain and prevent further tissue damage.

Rapid Eye Movement (REM) Sleep The part of the sleep cycle when active dreaming takes place. It is characterized by neocortical EEG waves similar to those observed during waking. This state is accompanied by paralysis of the body's muscles; only the muscles that allow breathing and control eye movements remain active.

Reflexes Considered the simplest and most fundamental movements, they are relatively fixed, automatic muscle responses to particular stimuli, such as the slight extension of the leg when a physician taps the knee with a small rubber hammer.

Retina A multilayered sensory tissue that lines the back of the eye and contains the receptor cells to detect light.

Reuptake A process by which released neurotransmitters are absorbed for later reuse.

Rods A sensory neuron located in the periphery of the retina. The rod is sensitive to light of low intensity and is specialized for nighttime vision.

Saltatory Conduction The process by which action potentials "jump" along the unmyelinated nodes of Ranvier, speeding electrical transmission.

Schizophrenia A chronic disorder characterized by psychosis (e.g., hallucinations and delusions), flattened emotions, and impaired cognitive function.

Schwann Cell A type of glial cell in the peripheral nervous system that forms myelin.

Selective Serotonin Reuptake Inhibitors (SSRIs) Drugs that block the reuptake of serotonin, increasing its availability in the synapse. SSRIs are used to treat depression and other disorders.

Semantic Memory A type of declarative memory that involves memory of facts.

Serotonin A monoamine neurotransmitter believed to play many roles, including but not limited to temperature regulation, sensory perception, and the onset of sleep. Neurons using serotonin as a transmitter are found in the brain and gut. Several antidepressant drugs are targeted to brain serotonin systems.

Short-Term Memory A phase of memory in which a limited amount of information may be held for several seconds or minutes.

Somatosensory Cortex A region of the parietal lobe responsible for processing touch and pain signals from the body.

Spinal Cord A bundle of nerve fibers running through the vertebral column that primarily functions to facilitate communication between the brain and the rest of the body.

Stem Cells Unspecialized cells that renew themselves for long periods through cell division.

Stress Any external stimulus that threatens homeostasis. Many kinds of stress have a negative effect on the body, but some kinds can be helpful.

Striatum A cluster of neurons deep within the brain divided into ventral and dorsal regions. The ventral striatum consists of the nucleus accumbens and the olfactory tubercle, while the dorsal striatum consists of the caudate and putamen. The striatum is a part of the basal ganglia and is involved in reward processing.

Stroke A block in the brain's blood supply. A stroke can be caused by the rupture of a blood vessel, a clot, or pressure on a blood vessel (as may be caused by a tumor). Without oxygen, neurons in the affected area die, and the part of the body controlled by those cells cannot function. A stroke can result in loss of consciousness and death.

Substantia Nigra A region of the midbrain involved in movement and reward. Parkinson's disease destroys the dopamine-producing neurons in this region.

Suprachiasmatic Nucleus (SCN) A small group of nerve cells in the hypothalamus that express clock proteins, which go through a biochemical cycle of about 24 hours. This sets the pace for daily cycles of activity, sleep, hormone release, and other bodily functions.

Sympathetic Branch A branch of the autonomic nervous system responsible for mobilizing the body's energy and resources during times of stress and arousal.

Synapse A physical gap between two neurons that functions as the site of information transfer from one neuron to another.

Synaptic Plasticity The ability of synapses to alter their strength by changing their size, shape, number of receptors, and amount of neurotransmitter released.

Synaptic Pruning The elimination of weak or non-functioning synapses to fine-tune neural circuitry.

Taste Buds A sensory organ found on the tongue.

Temporal Lobes One of the four major subdivisions of each hemisphere of the cerebral cortex. The temporal lobe functions in auditory perception, speech, and complex visual perceptions.

Testosterone A sex hormone produced primarily in the testes but also in lower amounts in the adrenal cortex and ovaries.

Thalamus A structure consisting of two egg-shaped masses of nerve tissue, each about the size of a walnut, deep within the brain. The key relay station for sensory information flowing into the brain, the thalamus filters out information of particular importance from the mass of signals entering the brain.

Trophic Factors Small proteins in the nervous system that are necessary for the development, function, and survival of specific groups of neurons.

Vagus Nerve The tenth cranial nerve, it transmits signals from the brain to the heart, lungs, and digestive tract.

Voluntary Movement A motor action that is consciously planned and executed.

Wernicke's Area A region in the temporal lobe responsible for comprehension of language.

White Matter The part of the brain that contains myelinated nerve fibers. The white matter gets its color from myelin, the insulation covering nerve fibers.

Working Memory A temporary type of declarative memory, the ability to keep a piece of information "in mind." It is limited to a small amount of data and, unless transferred to long-term memory, decays within a few seconds.

Neuroscience Resources

The Society for Neuroscience
1121 14th Street NW, Suite 1010
Washington, DC 20005
(202) 962-4000
sfn.org

Neuroscience Partner Organizations

Canadian Association for Neuroscience
can-acn.org

Canadian Institutes of Health Research
cihr-irsc.gc.ca

Dana Alliance for Brain Initiatives
dana.org

Faculty for Undergraduate Neuroscience
funfaculty.org

Federation of European Neuroscience Societies
fens.org

Foundation for Biomedical Research
fbresearch.org

Gatsby Charitable Foundation
gatsby.org.uk

International Brain Research Organization
ibro.info

La Sociedad Mexicana de Ciencias Fisiológicas (Mexican Society of Physiological Sciences)
smcf.org.mx

Lundbeck Foundation
lundbeckfonden.com

The Kavli Foundation
kavlifoundation.org

Stanley Center at Broad Institute
broadinstitute.org/stanley

Wellcome Trust
wellcome.ac.uk

U.S. National Institutes of Health (NIH)

nih.gov

NIH Institutes and Centers

National Eye Institute
nei.nih.gov

National Heart, Lung and Blood Institute
nhlbi.nih.gov

National Institute on Aging
nia.nih.gov

National Institute on Alcohol Abuse and Alcoholism
niaaa.nih.gov

National Institute of Biomedical Imaging and Bioengineering
nibib.nih.gov

National Institute of Child Health and Human Development
nichd.nih.gov

National Institute on Deafness and Other Communication Disorders
nidcd.nih.gov

National Institute of Dental and Craniofacial Research
nidcr.nih.gov

National Institute on Drug Abuse
nida.nih.gov

National Institute of Environmental Health Sciences
niehs.nih.gov

National Institute of General Medical Sciences
nigms.nih.gov

National Institute of Mental Health
nimh.nih.gov

National Institute of Neurological Disorders and Stroke
ninds.nih.gov

National Institute of Nursing Research
ninr.nih.gov

National Library of Medicine
nlm.nih.gov

National Center for Advancing Translational Sciences
ncats.nih.gov

National Center for Complementary and Integrative Health
nccih.nih.gov

U.S. National Science Foundation

nsf.gov

World Health Organization

who.int

Index

N

O

P

Q

R

S

T

U

V

W

BrainFacts.org

FOUNDING PARTNERS

The Kavli Foundation

The Kavli Foundation, established by Fred Kavli, is dedicated to advancing science for the benefit of humanity, promoting public understanding of scientific research, and supporting scientists and their work. The Foundation's mission is implemented through an international program of research institutes in the fields of astrophysics and theoretical physics, nanoscience, and neuroscience, and through the support of conferences, symposia, endowed professorships, journalism workshops, and other activities. The Foundation is also a founding partner of the Kavli Prizes, biennial $1 million prizes that recognize scientists for their seminal advances in three research areas: astrophysics, nanoscience, and neuroscience.

Gatsby Charitable Foundation

Gatsby is a trust set up by David Sainsbury to realize his charitable objectives in plant science research, neuroscience research, science and engineering education, economic development in Africa, public policy research and advice, and the arts.

Gatsby aims to be more than a funder, acting as an enabler for projects, designing, developing, overseeing and, in some cases, delivering activities. Gatsby takes a long-term view as they do not think much can be achieved by short, one-off projects. Gatsby is always looking to increase the impact of its limited funds, and is therefore eager to form partnerships with others who share its goals. Gatsby supports both large- and small-scale work, employing different methods and models depending on the different challenges, but is always ultimately looking to deliver long-term, sustainable change.

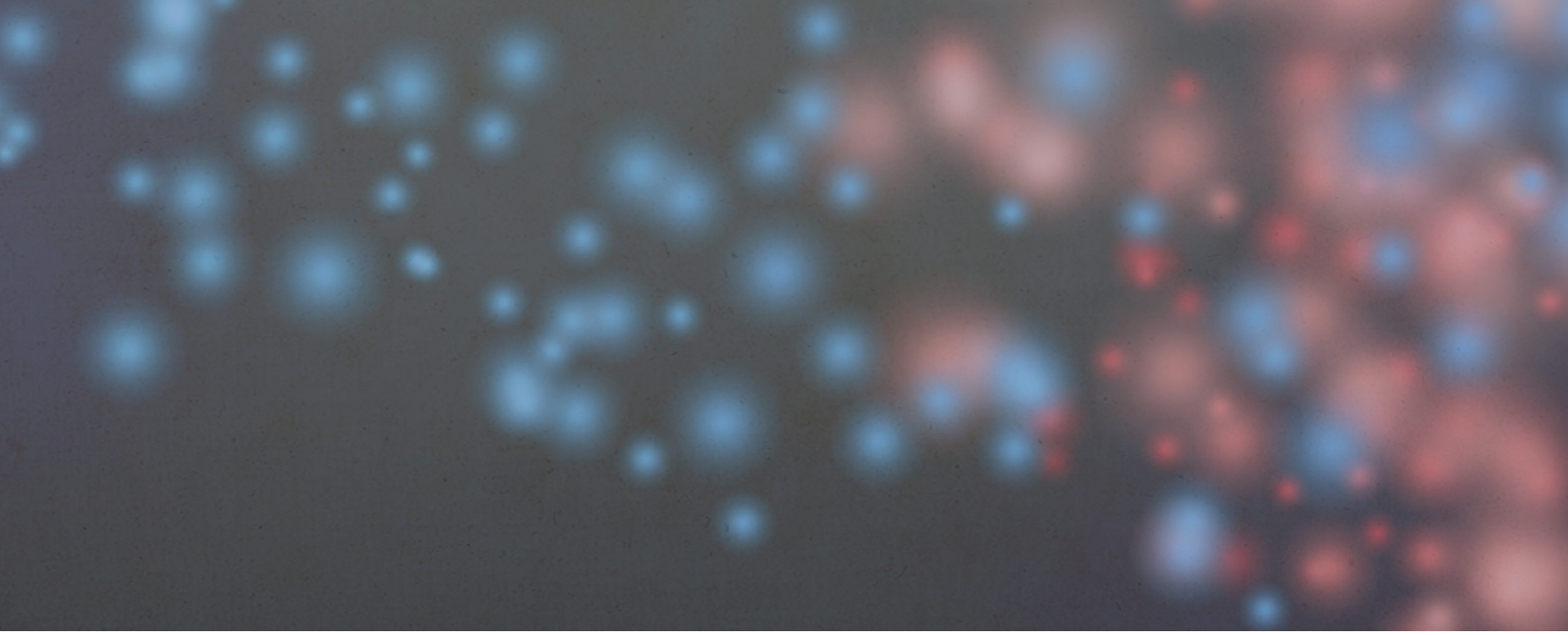
Society *for* Neuroscience

The Society for Neuroscience (SfN) is the world's largest organization of scientists and physicians devoted to understanding the brain and nervous system. The nonprofit organization, founded in 1969, now has nearly 37,000 members in more than 90 countries and over 130 chapters worldwide.

SfN's mission is to:

- Advance the understanding of the brain and the nervous system by bringing together scientists of diverse backgrounds, by facilitating the integration of research directed at all levels of biological organization, and by encouraging translational research and the application of new scientific knowledge to develop improved disease treatments and cures.
- Provide professional development activities, information, and educational resources for neuroscientists at all stages of their careers, including undergraduates, graduates, and postdoctoral fellows, and increase participation of scientists from a diversity of cultural and ethnic backgrounds.
- Promote public information and general education about the nature of scientific discovery and the results and implications of the latest neuroscience research. Support active and continuing discussions on ethical issues relating to the conduct and outcomes of neuroscience research.
- Inform legislators and other policymakers about new scientific knowledge and recent developments in neuroscience research and their implications for public policy, societal benefit, and continued scientific progress.

SfN's mission emphasizes the importance of engaging and inspiring the public about the progress and promise of brain research. BrainFacts.org, a public information initiative of The Kavli Foundation, the Gatsby Charitable Foundation, and SfN, provides trusted, authoritative information to the public about the brain and nervous system.



A Companion Publication to

BrainFacts.org

A PUBLIC INFORMATION INITIATIVE OF:

THE KAVLI FOUNDATION

GATSBY

SfN SOCIETY *for* NEUROSCIENCE

The Society for Neuroscience | 1121 14th Street NW | Suite 1010 | Washington, DC 20005 | (202) 962-4000 | sfn.org