

Summary of Research Activities by Disease Categories

Neuroscience and Disorders of the Nervous System

In 1953, when 27-year-old Henry M. (H.M.) turned to brain surgery to end his struggles with intractable epilepsy, he unwittingly ushered in a new era in research and understanding of memory and the brain. After determining the origin of H.M.'s seizures, neurosurgeon William Scoville removed portions of his brain containing and surrounding a structure called the hippocampus. The operation successfully quieted H.M.'s seizures but left him with profound amnesia—an unintended consequence that fascinates neuroscientists to this day. H.M. retained his former intelligence, his perceptual and motor abilities, and, most notably, his memory of early life events. Yet his recall of new events since the time of the surgery is only fleeting: he still believes he is about 30 years old and, even after many introductions, greets people in his life as though they have never met. Over the last 50 years, some 100 investigators have examined H.M.'s case. Their observations, as well as studies of patients with damage in similar brain regions, including those with Alzheimer's disease, have revolutionized understanding of how memories are formed and where in the brain they are stored. Today, these insights both guide and are extended by human brain imaging studies during learning and memory tasks and by investigations in animals at the level of single neurons and even molecules, leading to the development of drugs to treat memory deficits in people.

Introduction

Composed of the brain, spinal cord, and nerves of the body, the nervous system underlies perception, movement, emotions, learning and memory, and other functions essential to individual and societal well-being. The nervous system interacts with all other organ systems and is affected by countless diseases, conditions, and environmental factors. Moreover, with limited capacity for self-repair, the nervous system is particularly vulnerable to damage due to injury or infection, and its repair mechanisms are poorly understood. Neuroscience research seeks to understand the nervous system and its functions in health and disease. Given its intrinsic complexity and central role in physiology and behavior, this understanding must necessarily come from multiple perspectives. Accordingly, neuroscience research spans many disciplines, from genetics to physiology to psychology, and applies tools from areas such as molecular biology, anatomy, computer science, and imaging technologies.

Neuroscience is a unifying theme in NIH research. The intramural and extramural programs of several ICs have a major focus on the nervous system, but the full scope of neuroscience activities extends to components of research portfolios across most of NIH, reflecting the multidisciplinary nature of the field and the importance of the nervous system to many aspects of human health, development, and disease. These activities often involve collaborative efforts combining the unique strengths and expertise of individual ICs. NIH established the [Blueprint for Neuroscience Research](#)¹¹ to reinforce such collaboration and to accelerate neuroscience research through training initiatives and the development of shared tools and resources.

¹¹Institutes and Centers participating in the NIH Blueprint for Neuroscience Research: NEI, NIA, NIAAA, NIBIB, NCCAM, NICHD, NCRR, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, and OBSSR.

The principal aim of NIH research in neuroscience is to reduce the burden of diseases that affect the nervous system, including a broad range of neurological disorders; disorders affecting cognitive, emotional, and behavioral function; diseases and conditions that impair the primary senses; and developmental and age-related disorders. Whether led by single investigators or conducted through centers and consortia, NIH neuroscience research includes basic science studies of normal function and development in both humans and animal models, translational research that develops medications or other therapies, and clinical trials that test interventions in patients.

Nervous system disorders include common killers and major causes of disability like stroke, multiple sclerosis, and epilepsy, as well as hundreds of less common diseases, such as lysosomal storage disorders, spinal muscular atrophy, muscular dystrophies, neurofibromatosis, tuberous sclerosis, and Rett and Tourette syndromes. Many neurological disorders have genetic or developmental origins. Others result from trauma to the nerves, spinal cord, or brain; from autoimmune, infectious, or systemic disease; from tumor growth in nervous system tissues (see the section “Cancer”); or from neurodegenerative processes as in Parkinson’s disease, frontotemporal dementia, and amyotrophic lateral sclerosis (ALS). NIH research on neurological diseases, largely supported by NINDS, seeks to uncover their causes and mechanisms and to develop drugs and other treatments or preventive strategies. This research also aims to understand the multiple aspects of the nervous system that disease can affect and has shared support across NIH for basic science studies of the cerebral vasculature, electrochemical signaling in neurons and other cells, mechanisms of development and cell death, neuromuscular function and motor control, and behavior and cognition. In addition, NIH works to enhance the lives of those disabled by stroke, traumatic brain injury, spinal cord injury, and other neurological conditions through research, supported by NICHD’s [National Center for Medical Rehabilitation Research](#) and other ICs, on neuroplasticity, recovery and repair of motor and cognitive function, and rehabilitative and assistive strategies and devices (see the section “Life Stages, Human Development, and Rehabilitation”).

Brain disorders affecting cognitive, emotional, and behavioral function include schizophrenia and psychoses; autism and other developmental disorders; mood and anxiety disorders; and addiction to nicotine, alcohol, and other substances; as well as posttraumatic stress disorder, eating disorders, attention deficit hyperactivity disorder, and other behavioral disorders. These disorders have complex causes involving genetic and environmental influences and their interactions throughout life. Through research efforts led by NIAAA, NIDA, and the National Institute of Mental Health (NIMH), NIH focuses on uncovering these causes, understanding their neural and behavioral bases, and developing therapies and interventions for treatment and prevention. NIH research also seeks to understand the acute and long-term effects of abused substances on the nervous system.

Sight, smell, balance and our other primary senses, as well as the ability to communicate allow interactions with a changing external environment. The National Eye Institute (NEI) and the National Institute on Deafness and Other Communication Disorders (NIDCD) sponsor most of NIH’s research on basic mechanisms of sensory perception and communication and on diseases and conditions affecting the eyes and vision, hearing and balance, speech and language, taste and smell, and somatosensory function, including the senses of temperature and touch. Although vital to survival, the sensation of pain is also symptomatic of many diseases with origins in and outside the nervous system, from migraine and other headaches to chronic pain in cancer. NIH pain research is led by NIDCR and the [NIH Pain Consortium](#), which coordinates research across NIH on pain and its treatment (see the section “Chronic Diseases and Organ Systems”). NIH-supported research also studies the many ways the nervous system interacts with and regulates changes in the body’s internal environment. This research, including efforts supported by NHLBI and NIDDK, focuses on areas such as circadian rhythms and sleep disorders; neuroendocrine processes that regulate stress responses, hormone levels, and motivational states; and the neural basis of appetite and feeding, which is of key relevance to slowing the increasing rates of obesity worldwide.

Nervous system disorders may arise in development, strike young adults, or emerge late in life. NICHD and other ICs sponsor research on the development of the nervous system and its functions. This research encompasses studies of structural birth defects, including spina bifida and other neural tube defects and associated conditions such as hydrocephalus. NIH also invests in research on developmental disorders like cerebral palsy, Down's syndrome, autism, and other causes of intellectual and learning disabilities. Nervous system development continues into early adulthood in humans, and developmental processes and their external influences contribute to mental fitness and disease risk later in life, including the risk for addiction, which often begins in childhood or adolescence. At the other end of the lifespan, with key support by NIA, NIH research on the aging nervous system includes studies of age-related disorders such as Alzheimer's disease and other dementias, as well as environmental and lifestyle factors affecting neurological, cognitive, and emotional health in aging populations.

Across all ages, the nervous system is a common target of exposure to toxins, pollutants, and other agents, whose effects range from acute reactions to developmental disorders and neurodegeneration. NIH-sponsored research on the consequences of such environmental exposures for nervous system function and disease includes a particular focus by NIEHS. NIH also considers diseases of the nervous system from a global point of view. Coordinated primarily by FIC, neuroscience-related research is supported by NIH in unique populations and environments and on factors contributing to disparities in disease vulnerability and treatment quality and access around the world, such as socioeconomic conditions and infectious disease.

The Burden of Nervous System Disorders

Nervous system disorders take an enormous toll on human health and the economy. Even rare disorders carry a substantial collective burden, as they often have an early onset and long duration, and the stigma commonly attached to neurological and mental illnesses further compounds individual and societal impact. According to 2005 estimates, neurological disorders strike more than 1 billion people worldwide, account for 12 percent of total deaths, and result in more disability than HIV/AIDS, ischemic heart disease, or malignant tumors¹². In the United States, stroke is the third leading killer of adults and results in annual medical and disability costs totaling over \$60 billion¹³. Another 1.4 million Americans sustain a traumatic brain injury each year; it is the leading cause of death and long-term disability in young adults¹⁴. Traumatic brain injury accounted for an estimated \$60 billion in direct medical costs and indirect costs in 2000¹⁵.

Although less often cited as direct causes of mortality, mental disorders result in more disability for U.S. adults than any other class of medical illness¹⁶, and mental illnesses other than drug abuse and addiction account for more than \$150 billion in costs annually¹⁷. In a given year, approximately 12.5 million American adults (or 1 in

¹² World Health Organization. *Neurological Disorders: Public Health Challenges*. Geneva: WHO Press, 2006.

¹³ [Rosamond W, et al. *Circulation* 2007;115:e69-171](#), PMID: 17194875

¹⁴ Langlois JA, Rutland-Brown W, Thomas KE. *Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths*. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2006.

¹⁵ Finkelstein E, Corso P, Miller T, et al. *The Incidence and Economic Burden of Injuries in the United States*. New York: Oxford University Press, 2006.

¹⁶ World Health Organization, 2006.

¹⁷ For more information, see <http://www.mentalhealthcommission.gov/reports/FinalReport/toc.html>

every 17) suffer mental illness symptoms so severe as to cause significant disability^{18, 19}. In 2005, 23.2 million Americans needed treatment for an alcohol or illicit drug use problem, and costs related to illicit drug use alone totaled about \$180 billion²⁰. Nervous system disorders also severely affect the lives of children; an estimated 17 percent of U.S. children have a developmental or behavioral disorder such as autism, intellectual disability, or attention deficit hyperactivity disorder²¹.

Demographic trends project an increasing burden from nervous system disorders. In particular, the prevalence of age-related diseases of the nervous system is expected to increase in aging populations benefiting from increased longevity. Current estimates of the number of U.S. adults with Alzheimer's disease range from 2.4 million to 4.5 million, and unless effective interventions are developed, this number is expected to rise almost threefold by 2050^{22, 23}.

NIH Funding for Neuroscience and Disorders of the Nervous System

In FYs 2006 and 2007, NIH funding for research in neuroscience and disorders of the nervous system was \$4.830 billion and \$4.809 billion respectively. The table at the end of this chapter indicates some of the research areas involved in this investment (see "Estimates of Funding for Various Diseases, Conditions, and Research Areas").

Summary of NIH Activities

Many common themes reflect shared biological processes found in many aspects of nervous system function and disease. Three such themes—neurodevelopment, neuroplasticity, and neurodegeneration—provide a useful perspective on the broad, multidisciplinary field of neuroscience research and illustrate the dynamic nature of the nervous system across the lifespan. In this section, these themes will serve to highlight selected examples of activities and progress in neuroscience research enabled by NIH, as well as challenges and future opportunities. Additional activities and initiatives exemplify how collaborative approaches are facilitating advances in basic, translational, and clinical neuroscience. More information, as well as more examples, may be found in the bulleted list at the end of this chapter.

Neurodevelopment: Periods of Growth, Maturation, and Vulnerability

Complex interactions between gene expression and function, endocrine and other physiological processes, neuronal activity, and external influences guide the development of the nervous system. From the early differentiation of its many neuronal and other cell types to the establishment of billions of connections, or

¹⁸ Kessler RC, et al. *Arch Gen Psychiatry* 2005;62:617-27, PMID: 15939839

¹⁹ For more information, see <http://www.census.gov/popest/national/asrh>

²⁰ Substance Abuse and Mental Health Services Administration. Results from the 2005 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-30, HHS Publication No. SMA 06-4194). Rockville, MD; 2006; For more information, see <http://oas.samhsa.gov/NSDUH/2k5NSDUH/2k5results.htm>

²¹ U.S. Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. The National Survey of Children with Special Health Care Needs Chartbook 2001. Rockville, MD: U.S. Department of Health and Human Services, 2004; For more information, see <http://www.cdc.gov/ncbddd/child/improve.htm>

²² Plassman BL, et al. *Neuroepidemiology* 2007;29:125-32, PMID: 17975326

²³ Hebert LE, et al. *Arch Neurol* 2003;60:1119-22, PMID: 12925369

synapses, between neurons, each step in nervous system development is vulnerable to disruption by disease, injury, or environmental exposures. Each also has implications for normal neurological, mental, and behavioral function and for health and disease risk across the lifespan.

Human brain development continues into early adulthood and proceeds at different rates in different brain areas and pathways. Understanding normal nervous system development is essential to identifying when, where, and how developmental processes can go wrong. To this end, NIH-supported investigators are applying advanced brain imaging technologies to large-scale studies of human brain development in healthy children and adolescents. For example, in the [NIH Magnetic Resonance Imaging \(MRI\) Study of Normal Brain Development](#), extramural researchers at seven collaborating institutions are collecting brain scans and clinical and behavioral data from more than 500 infants, children, and adolescents over the course of 7 years. Data gathered and analytical tools developed for this longitudinal study will be available to the broader research community in a Web-based, searchable database.

As another example, in the largest longitudinal pediatric neuroimaging study to date (829 MRI scans from 387 subjects, ages 3 to 27 years), intramural NIH scientists have reported different trajectories of brain development in males and females, finding that brain volume peaks earlier in girls than in boys. Such studies of normal brain development and maturation are providing scientists with important baseline data that will help them identify signs of atypical development as well as factors that may be associated with disease risk later in life. Moreover, understanding the developmental course of different brain areas can help to explain behavioral and cognitive development and its consequences for mental health and disease risk. For instance, previous brain imaging studies have suggested that brain pathways that are important for decision-making and impulse control are among the last to fully mature. This aspect of brain development may contribute to impulsive behavior in teenagers and help explain their increased susceptibility to drug abuse and addiction.

In a remarkable feat of nervous system development, the estimated 100 billion neurons in the human brain are wired together into networks that underlie brain functions, from sensory perception, to learning and memory, to motor control. Insight into the wiring diagrams of these networks and the developmental processes that lead to their establishment promises to unlock some of the most fundamental questions in neuroscience research. Indeed, certain brain diseases, including schizophrenia and autism, are hypothesized to involve aberrant development of brain connectivity. Research in this area benefits from new technologies for manipulating and visualizing neurons in experimental animal models, in which neuronal connections are established and organized according to rules similar to those found in the human nervous system. In one recent example, NIH-supported scientists developed a technique that can label thousands of direct synaptic connections received by individual neurons in the rat brain. By enabling neuroscientists to map neuronal networks, such experimental techniques will help show how changes in brain function and behavior can result from changes in these networks, whether they occur during normal development and learning or as a consequence of injury or disease.

One salient feature of the developing nervous system is its heightened sensitivity to external influences. Although crucial for shaping the proper development of many brain pathways and their corresponding sensory, motor, cognitive, and emotional functions, this heightened sensitivity also makes the developing nervous system especially vulnerable to potentially damaging environmental factors. These factors include exposures to toxins, viral infections, nutritional deficits, traumatic events, and social experiences throughout life. For instance, prenatal exposure to alcohol can lead to fetal alcohol syndrome (FAS), a devastating developmental disorder characterized by lifelong nervous system impairments that may include intellectual and learning disabilities, and behavioral and social deficits. NIH supports a broad research portfolio on FAS and its diagnosis, treatment, and prevention. A growing area of neuroscience research focuses on how genetic and environmental factors interact in nervous system development, function, and disease. The interplay between external influences and genetic predispositions

appears likely to contribute to a range of disorders, such as depression and other mood and anxiety disorders, addiction, multiple sclerosis, Parkinson's disease, and autism. As one example of research in this area, NIH supports several efforts to understand how autism spectrum disorders may arise from the combined effects of genetic vulnerabilities and exposure to harmful environmental agents during key periods of development. Ongoing projects co-funded by NIH and the Environmental Protection Agency (EPA) are looking for biomarkers of these disorders and for differences in immune system function that may increase susceptibility to potential environmental triggers.

Neuroplasticity: Substrates for Change and Repair

Throughout development, and even once its basic structure and circuitry have been established, the nervous system retains a remarkable capacity to adapt to or be affected by changes in the body's internal environment and external conditions and events. This capacity, known as *plasticity*, results in changes in the electrical activity and composition of neuronal networks. Plasticity occurs at many levels of the nervous system, from altered signaling at synapses thought to underlie learning and memory, to large-scale functional and neuroanatomical reorganization accompanying the loss of a limb or sensory organ.

Neuroplasticity enables beneficial adaptations, including acquiring new knowledge, improving performance on practiced tasks, and adjusting behavior based on positive or rewarding consequences. A recent NIH-funded study demonstrated how such adaptive plasticity might be exploited for therapeutic intervention. In this study, using real-time brain imaging, patients with chronic pain learned to exert voluntary control over activation of a particular brain region involved in pain perception and its regulation, effectively reducing the impact of their painful sensations. Unfortunately, plasticity can also be maladaptive. Accumulating evidence from NIH-supported research indicates that the same brain mechanisms that mediate reward-related learning are involved in the development of addiction and compulsive overeating. Continued research into how plasticity contributes to addiction and other mental disorders may lead to intervention strategies that reverse or prevent these mechanisms.

Neuroplasticity also plays a role in many aspects of epilepsy, a class of disorders characterized by abnormal bursts of electrical activity (seizures) in networks of neurons that can lead to odd sensations, emotions, behaviors, convulsions, muscle spasms, and loss of consciousness. Basic neuroscience studies on the plasticity of synaptic connections and brain circuits are showing how epileptic activity emerges and how seizures themselves can in turn cause plasticity in affected circuits, often increasing the probability of seizure recurrence. In addition to these basic science studies, NIH supports translational research and clinical trials of potential anticonvulsant therapies, including extensive efforts through the [NIH Anticonvulsant Screening Program](#), a drug discovery program that conducts state-of-the-art evaluations to determine both potential efficacy and toxicity of preclinical candidate compounds in validated epilepsy model systems. NIH also works with the epilepsy community to develop and pursue benchmarks for research to prevent and treat epilepsy and co-occurring disorders.

Harnessing the capacity of the nervous system to adapt by activating its intrinsic mechanisms for repair and plasticity offers great hope for restoring function in the injured or diseased brain and spinal cord. For example, after spinal cord injury, neurons near the site of damage sprout new nerve fibers. Although this sprouting is limited in the absence of intervention, an understanding of the mechanisms that guide and restrict such spinal plasticity may allow neuroscientists to design strategies that integrate the new nerve fibers into spinal circuitry, replacing damaged connections and promoting functional recovery. In addition, NIH has long supported a program to develop neural prostheses, devices that restore functions that have been lost due to injury or disease, as in deafness or paralysis from spinal cord injury. The success of neural prostheses depends not only on their ability to bypass or replace injured components of the nervous system, but also on their integration into remaining functional circuits, which relies on plasticity mechanisms.

Stem cells are another promising source of plasticity and repair in the nervous system, and although many challenges and questions remain in this young area of research, basic and translational neuroscience studies are making progress in advancing stem cell-based therapies toward the clinic. During early embryonic development, stem cells have the potential to become any cell type in the body; as development proceeds, the range of potential fates narrows, depending on the tissue generating the cells. Beyond early development, stem cell production and neurogenesis—the generation of new neurons—occurs only in restricted regions of the brain. One active area of basic neuroscience research examines the role of neural stem cells in normal function and the brain’s response to injury and disease, and the potential for treatments that tap into this intrinsic renewal mechanism. Other stem cell research in neuroscience focuses on the development of therapies in animal models that transplant stem cells into the damaged or diseased nervous system. Transplanted cells may be embryonic stem cells or other non-neuronal stem cells, they may be engineered to become certain desired cell types, or they may be designed to express specific genes that could act to promote recovery or repair or restore genetic deficits. As part of the [Quantum Grants Program](#) designed to make profound advances in health care, NIH has recently funded research to engineer implants from neural and vascular stem cells and innovative biomaterials to provide a source of cells for tissue repair in an animal model of stroke.

Neurodegeneration: Fighting the Effects of Age, Exposure, and Disease

The progressive loss of neurons is a common endpoint of many diseases and insults to the nervous system. Such degeneration presents challenges to developing strategies to slow and prevent cell death, protect remaining neurons, and possibly replenish those that are lost. Although recent and ongoing research continues to yield exciting insights into the biological and environmental causes of neurodegenerative disorders, much remains unexplained, and while some interventions alleviate disease symptoms, none currently exists that can halt progressive degeneration.

Aging is the most consistent risk factor for developing a neurodegenerative disorder, and many of the 50 million adults in the United States who are older than age 60 are at substantial risk for cognitive impairment and emotional disorders from many causes as they age. The trans-NIH [Healthy Brain Project](#) focuses on demographic, social, and biologic determinants of cognitive and emotional health in aging adults. The risk for degenerative disorders affecting sensory systems also increases with age, leading to hearing and visual impairments. Building on a previous demonstration that antioxidant supplements could slow age-related macular degeneration (AMD), the leading cause of blindness in the elderly, a large-scale NIH study is assessing the benefits of other supplements and dietary changes on AMD and cataracts.

Alzheimer’s disease is the most common cause of dementia in the elderly, though some inherited forms of the disease become symptomatic in middle age, and scientists now believe that damage to the brain begins well before symptoms appear. Basic science studies have identified genetic factors and protein abnormalities that contribute to neuronal dysfunction and death in Alzheimer’s disease. NIH also funds 29 [Alzheimer’s Disease Centers](#), which carry out clinical studies and other research on Alzheimer’s and related degenerative diseases (see Chapter 4). In addition, NIH supports clinical trials for treating and slowing Alzheimer’s disease, many of which are coordinated through the [Alzheimer’s Disease Cooperative Study](#), which involves nearly 70 sites in the United States and Canada. Ongoing trials include the Docosahexaenoic Acid trial, which is examining whether treatment with DHA, an omega-3 fatty acid, will slow decline in patients with Alzheimer’s disease. Observational studies have shown a reduced risk of Alzheimer’s disease associated with DHA consumption, and animal studies have shown that DHA reduces brain levels of beta-amyloid, oxidative damage associated with beta-amyloid, and neurotoxicity. Recent research has also shown that an extract from the leaf of the *Ginkgo biloba* tree reduces neuronal pathology and symptoms in an animal model of the disease, and NIH is supporting the largest clinical trial to date to test the

effectiveness of *Ginkgo biloba* in preventing dementia in humans. Additional research supported through the [Alzheimer's Disease Neuroimaging Initiative](#) aims to identify biomarkers and develop imaging technologies to aid early diagnosis, which may enable more targeted and timely interventions.

Neurodegenerative disorders are often associated with degeneration in specific populations of neurons or regions of the nervous system. For example, Parkinson's disease results in the loss of a class of dopamine-producing neurons in the substantia nigra, a part of the brain important for motor control. NIH-funded scientists recently described a mechanism in substantia nigra neurons that contributes to their selective vulnerability and that, like the disease itself, becomes more prevalent with age. Manipulations to "rejuvenate" the neurons by blocking this mechanism promoted their survival, suggesting a new potential target for drug development. NIH also supports 14 [Morris K. Udall Centers for Excellence in Parkinson's Disease](#) Research and engages with the Parkinson's disease research community to identify and pursue research opportunities.

Neurons are not unique in their vulnerability to degenerative disorders. Muscular dystrophies are a class of neuromuscular disorders that lead to progressive muscle weakness and degeneration. NIH support for research on muscular dystrophies includes funding for six [Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers](#) (see Chapter 4), as well as other efforts to translate basic science findings to the clinic. Multiple sclerosis is the most common of a number of diseases that lead to the degeneration of myelin, a fatty substance that ensheathes many nerve fibers in the brain. NIH-supported scientists recently reported the first genetic risk factors for multiple sclerosis to be identified in more than 20 years (see also the section "Autoimmune Diseases" in this chapter). These studies benefited from new technologies in genetic research that allow simultaneous analysis of many thousands of genetic variations, or polymorphisms, across the entire genome. Such genome-wide studies are giving scientists unprecedented insight into disorders that result from the combined effects of many genetic variations and their interactions with environmental influences.

Advancing Neuroscience Research Through Collaboration

The melding of disciplines involved in the study of the nervous system and the overarching themes linking its many functions and disorders make neuroscience a naturally collaborative field of research. Today's fast global communication and the power and storage capacity of modern computer systems are enabling collaborative research on increasingly large scales. A major priority of the [NIH Blueprint for Neuroscience Research](#) is to facilitate research by funding the creation of shared resources and tools for scientists. Examples include a publicly available atlas of gene expression in the mouse brain and spinal cord across the lifespan, a clearinghouse for informatics tools and resources for brain imaging applications, and an effort to develop common measures of neurological and behavioral function for use in clinical trials and epidemiological and longitudinal studies. NIH also supports several data registries, databases, and tissue consortia for neurological diseases and mental disorders that offer shared access to genetic and clinical data and biological samples. Genome-wide and other genetic studies using such materials are identifying genes that contribute to bipolar disorder, that influence the effectiveness of antidepressant therapies, and that predispose individuals to drug abuse and addiction (see also the section "Genomics" in Chapter 3).

Collaborative approaches are also transforming clinical and translational research in neuroscience, which build on advances and knowledge gained through basic science studies to develop treatments and interventions for disease in people. NIH supports seven centers as part of the [Specialized Program of Translational Research in Acute Stroke](#), a national network of research centers established to develop acute stroke therapies from preclinical research through early-phase clinical trials. These centers also work to improve prehospital stroke care, participate in community education, and develop telemedicine to expand rapid access to acute stroke care. NIH also supports the Silvio O. Conte Centers for the Neuroscience of Mental Disorders, which integrate and translate basic and

clinical neuroscience research on severe mental illnesses, such as schizophrenia and mood disorders. As another example, the [Spinal Muscular Atrophy \(SMA\) Project](#) is a new translational approach to preclinical drug development, motivated by the recent discovery of the gene defect that causes this degenerative disease that affects motor neurons of the spinal cord. With expertise from NIH as well as FDA, academia, and industry, the SMA Project has created a multisite enterprise for accelerated drug development.

Scientific research is an increasingly global endeavor, and because brain disorders are the leading contributors to disability in almost all parts of the world, global capacity for neuroscience research is essential. Through a program entitled [Brain Disorders in the Developing World](#), NIH supports innovative, collaborative programs to build sustainable neuroscience research capacity in low- and middle-income nations. Projects focus on some of the unique challenges facing neuroscience research in the developing world and on topics that are relevant worldwide, including the neurological consequences of infectious diseases and nutritional deficits. For example, one study suggests that a form of the APOE4 gene, which is associated with an increased risk for developing Alzheimer's disease, may have a protective effect early in life against the negative consequences of malnutrition. This finding may help elucidate mechanisms to protect the brain and body during times of nutritional deficit.

Looking to the Future

NIH-supported neuroscience research is steadfastly advancing its mission to reduce the burden of nervous system disorders. New technologies that allow neuroscientists to observe and manipulate neuronal networks could provide insights into how neural activity leads to complex brain functions. Continued innovation in neuroimaging techniques may identify disease risk or presence early, enabling more rapid diagnosis and intervention. With knowledge gained through large-scale genetic and epidemiological studies, clinicians of the future may personalize preventive and therapeutic strategies according to the genetic profile and lifestyle of individual patients. Future medications for treating nervous system disorders may reach specific brain targets with ease, and advances in neuroprostheses may more successfully restore motor, sensory, and cognitive function after disease or injury. These are just a few of the possibilities to come as NIH-supported neuroscience research continues to build on past progress and identify and pursue new opportunities. A glimpse into the future might reveal the ability to replenish damaged nerve cells, reprogram neuronal connections that support addiction, and stop degenerative processes that rob millions of their thoughts and memories.

Notable Examples of NIH Activity

Key for Bulleted Items:

E = Supported through Extramural research

I = Supported through Intramural research

O = Other (e.g., policy, planning, or communication)

COE = Supported through a congressionally mandated Center of Excellence program

GPRA Goal = Concerns progress tracked under the Government Performance and Results Act

Neurodevelopment: Periods of Growth, Maturation, and Vulnerability

Research on Environment and Autism: NIH has several innovative research studies aimed at understanding how autism and autism-spectrum disorders may arise from a combination of genetic vulnerability and exposure to harmful environmental agents during key periods of early development. The NIEHS/EPA Children's Center for

Environmental Health at the University of California, Davis supports a highly integrated research program spanning human-to-animal cellular models to explore the interplay of immune, genetic, and environmental factors in autism susceptibility. In 2001, this center launched the first and most comprehensive large-scale epidemiological investigation of environmental exposures and susceptibility factors for autism, the Childhood Autism Risk from Genes and Environment (CHARGE) study. Scientists are exploring how persistent organic pollutants such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) may contribute to neurological development disorders such as autism by interacting with cellular epigenetic mechanisms that control timing and patterns of gene expression. NIH also supports an exploratory study at Johns Hopkins University to develop new methods to measure individual differences in the immunotoxicity of mercury.

- For more information, see <http://www.vetmed.ucdavis.edu/cceh>
- (E/COE) (NIEHS)

Autism Centers of Excellence (ACE): In 2007 and 2008, NIH created the unified ACE program in order to maximize coordination and cohesion of NIH-sponsored autism research efforts. The ACE programs will focus on a broad range of autism-related research, including but not limited to neuroimaging, biomarkers and susceptibility genes, pharmacotherapy, early intervention, and risk and protective factors.

- For more information, see Chapter 4: *NIH Centers of Excellence*.
- (E) (NIMH, NICHD, NIDCD, NIEHS, NINDS)
- (COE)

National Database for Autism Research (NDAR): NDAR is a collaborative biomedical informatics system being created by NIH to provide a national resource to support and accelerate research in autism.

- For more information, see <http://ndar.nih.gov>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E/I) (NIMH, CIT, NICHD, NIDCD, NIEHS, NINDS)

Genomic Studies of Autism: NIH has supported a number of studies that are pointing to potential genetic causes of autism.

- For more information, see <http://www.nimh.nih.gov/press/gene-mutations-autism.cfm>
- For more information, see <http://www.nimh.nih.gov/press/largest-ever-search-for-autism-genes-reveals-new-clues.cfm>
- For more information, see <http://www.nimh.nih.gov/press/autismmetgene.cfm>
- For more information, see <http://www.nimh.nih.gov/press/moy-crawley-autism.cfm>
- This example also appears in Chapter 3: *Genomics*.
- (E) (NIMH, NCRR, NICHD, NINDS)

New Genetics Tools Shed Light on Addiction: NIH-supported research is taking full advantage of the massive databases and rapid technologies now available to study how genetic variations influence disease, health, and behavior. Such genetic studies are critical to teasing apart the molecular mechanisms and genetic predispositions underlying diseases like addiction. Investigators studying various neurological and psychiatric illnesses have already linked certain genes with specific diseases by using custom screening tools known as “gene chips” (e.g., the *neurexin* gene has been found to play a role in drug addiction). A next-generation “neurochip” is being developed with 24,000 gene variants related to substance use and other psychiatric disorders. Applying this tool to addiction

and other brain disorders will advance our understanding not only of vulnerability to addiction and its frequent comorbidities, but also of ways to target treatments based on a patient's genetic profile (i.e., a "pharmacogenetic" approach). To complement these efforts, NIH is investing heavily in the emerging field of *epigenetics*, which focuses on the lasting modifications to the DNA structure and function that result from exposure to various stimuli. Attention to epigenetic phenomena is crucial to understanding the interactions between genes and the environment, including the deleterious long-term changes to brain circuits from drug abuse. A focus on gene-by-environment interactions has recently been expanded to incorporate developmental processes, which are now known to also affect the outcome of these interactions. The resulting Genes, Environment, and Development Initiative (GEDI) seeks to investigate how interactions among these factors contribute to the etiology of substance abuse and related phenotypes in humans.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/rfa-da-07-012.html>
- For more information, see <http://nihroadmap.nih.gov/roadmap15update.asp>
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Technology Development*.
- (E/I) (NIDA, NCI, NIAAA, NIMH)
- (GPRA Goal)

Underage Drinking Research Initiative: In 2004, NIH launched the Underage Drinking Research Initiative with the goal of obtaining a more complete and integrated scientific understanding of the environmental, biobehavioral, and genetic factors that promote initiation, maintenance, and acceleration of alcohol use among youth, as well as factors that influence the progression to harmful use, abuse, and dependence, all framed within the context of overall development. Activities and accomplishments in 2007 include:

- Provided the scientific foundation for *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking* (released March 6, 2007) and for the ongoing work of the Interagency Coordinating Committee on Preventing Underage Drinking
 - Convened scientific meetings of experts, including the Underage Steering Committee that met four times over a 2-year period, a Meeting on Diagnosis of Alcohol Use Disorders Among Youth (April 2006), and a Meeting on Screening for Child and Adolescent Drinking and AUDs Among Youth (June 2007)
 - Issued three Requests for Applications (RFAs), including "Underage Drinking: Building Health Care System Responses" (four projects awarded in FY 2006), "Impact of Adolescent Drinking on the Developing Brain" (five projects awarded in FY 2007), and "Alcohol, Puberty, and Adolescent Brain Development" (three projects awarded in FY 2007).
 - Published Alcohol Research & Health, Vol. 28, Number 3: *Alcohol and Development in Youth: A Multidisciplinary Overview*
 - Published a supplement of seven developmentally focused papers covering a broad range of underage drinking topics (accepted for the journal *Pediatrics*).
- For more information, see <http://www.niaaa.nih.gov/AboutNIAAA/NIAAASponsoredPrograms/underage.htm>
 - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
 - (E) (NIAAA)

Prenatal Alcohol, Sudden Infant Death Syndrome, and Stillbirth (PASS) Research Network: Following a 3-year feasibility study, the NIH established this multidisciplinary consortium to determine the role of prenatal alcohol exposure and other maternal risk factors in the incidence and etiology of sudden infant death syndrome (SIDS), stillbirth, and fetal alcohol syndrome, all of which are devastating pregnancy outcomes. The PASS study will

prospectively follow 12,000 pregnant, high-risk, American Indian and South African women and their infants until the infants are 12 months old. Maternal, fetal, and infant measures and tissues will be obtained for analysis.

- For more information, see <http://www.nichd.nih.gov/research/supported/pass.cfm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NICHD, NIAAA)

The Role of Development in Drug Abuse Vulnerability: NIH supports a number of longitudinal studies at various stages of development, following cohorts over extended timeframes. Information is gathered on children's cognitive and emotional development, as well as their vulnerability to addiction later in life. These studies have been critical to estimate, for example, the contribution of in utero drug exposure to emotional and cognitive development, vulnerability to substance abuse, and other mental disorders. This knowledge, together with animal studies that provide complementary and validating information while minimizing the confounding factors that are likely to play a role in prenatal effects of drug exposure in humans, will help us to mitigate the deleterious impact of substance abuse on the developing fetus. With regard to later developmental stages, the application of modern brain imaging technologies has generated unprecedented structural and functional views of the dynamic changes occurring in the developing brain (from childhood to early adulthood). The discovery of these changes has been critical to understanding the role of brain development in decision-making processes and responses to stimuli, including early exposure to drugs. Such studies have suggested, for example, that an unbalanced communication between volitional control and emotional circuits may explain some of the impulsive reactions typical of adolescents, who tend to engage in risky behaviors and are at heightened risk for developing addictions. Collectively, these longitudinal studies, using new imaging and genetics tools, promise a greatly enhanced ability to interpret the effects of myriad environmental variables (e.g., quality of parenting, drug exposure, socioeconomic status, and neighborhood characteristics) on brain development and behavior.

- For more information, see http://www.drugabuse.gov/NIDA_notes/NNvol19N3/Conference.html
- For more information, see http://www.nida.nih.gov/NIDA_notes/NNvol19N3/DirRepVol19N3.html
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NIDA, NICHD) (GPRA Goal)

MRI Study of Normal Brain Development: Understanding healthy brain development is essential to finding the causes of many childhood disorders, including those related to intellectual and developmental disabilities, mental illness, drug abuse, and pediatric neurological diseases. NIH is creating the Nation's first database of MRI measurements and analytical tools, as well as clinical and behavioral data to understand normal brain development in approximately 500 children across the Nation. This large-scale, longitudinal study uses several state-of-the-art brain-imaging technologies. The data will be disseminated as a Web-based, user-friendly resource to the scientific community.

- [Evans AC, et al. *Neuroimage*. 2006;30:184-202, PMID: 16376577](#)
- For more information, see <http://www.bic.mni.mcgill.ca/nihpd/info/index.html>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E/I) (NICHD, NIDA, NIMH, NINDS)

Studies of Normal Brain Development: The NIH Intramural Research Program is conducting studies to explore

brain development in healthy children and adolescents with MRI. Recent studies have addressed brain structure differences related to risk for Alzheimer's disease and sex differences in brain development trajectories.

- [Shaw P, et al. *Lancet Neurol* 2007;6:494-500](#), PMID: 17509484
- [Lenroot RK, et al. *Neuroimage* 2007;36:1065-73](#), PMID: 17513132
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Epidemiological and Longitudinal Studies*.
- (NIMH) (GPRA Goal)

Powerful New Technique Reveals How Brain Cells Wire Together: In order to understand how the brain processes visual information and performs other tasks, researchers have wanted to construct a “wiring diagram” of the billions of neurons connected in precise, identifiable circuits. A breakthrough technology has helped clear this major hurdle by revealing all the connections made by a single nerve cell. The new tool uses a modified rabies virus, which can spread indefinitely through the nervous system by jumping between communicating nerve cells. However, scientists modified the virus so that it jumps once and then leaves a fluorescent tag in the neurons connected to a single cell. This permits visualization of functional processing circuits in living brains. It can also be used in transgenic mice to deactivate targeted classes of neurons expressing specific genes, revealing changes in brain function, including behavior.

- [Wickersham IR, et al. *Neuron* 2007;53:639-47](#), PMID: 17329205
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*
- (E) (NEI)

Neuroplasticity: Substrates for Change and Repair

Promising Approaches to Treating Chronic Pain: Opioid analgesics are the most powerful pain medications currently available; unfortunately, they can produce drug dependence. Thus, an area of enormous need is the development of potent non-opioid analgesics. In recognition of this, NIH has implemented an aggressive and multidisciplinary research program. Many of these initiatives are yielding tangible results that stand to revolutionize the field of pain management. At the molecular level, cannabinoid (CB) research has shown that it is possible to selectively activate the CB system to provide analgesia with minimal or no psychotropic side effects or abuse liability. New findings in basic pharmacology reveal previously unrecognized complexity emerging from the natural mixing of different receptors, the targeting of which could provide a vastly expanded range of pharmacotherapeutic effects. This approach has already ushered in the development of promising designer molecules that can block pain more selectively and safely. At the cellular level, active research on a non-neuronal brain cell type, glia, has led to the realization that glia activation can amplify pain. This discovery suggests that targeting glia and their pro-inflammatory products may provide a novel and effective therapy for controlling clinical pain syndromes and increasing the utility of analgesic drugs. At the brain circuit level, a new approach has been developed to harness the brain's intrinsic capacity to train itself through a strategy in which subjects “learn” how to regulate pain by viewing and then controlling images of their own brains in real time.

- For more information, see: <http://www.nida.nih.gov/whatsnew/meetings/default.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDA, NINDS)

Tools to Reveal the Mechanisms Governing Behavior: Newly acquired but rapidly evolving tools and techniques that monitor or probe discrete brain systems have allowed NIH-supported researchers to begin filling in the information gap between molecular or cellular events and behavioral outcomes. A notable preclinical example of

this trend is the development of a genetically engineered method to turn the electrical impulses of brain cells on and off with pulses of light—in sync with the split-second pace of real-time neuronal activity. The novel technique borrows genes from light-responsive algae and bacteria to unravel the intricate workings of brain circuits with extreme precision. This powerful new tool could be used to assess the role of neuronal activity in regulating normal behavior and disease processes. On the clinical side, an array of brain imaging devices has produced much information on how neural circuits develop and process information under normal conditions and how they become impaired by a disease like addiction. These advances have led to the fertile concept that the transition from abuse to addiction is not a switch but a gradual degradation of the ability of different circuits to “talk” to each other as they attempt to compensate for their deficiencies. Interestingly, these studies are also showing significant overlap in the circuits involved in drug abuse and the circuits underlying compulsive overeating and obesity. Moreover, in preclinical studies, compounds that interfere with food consumption in animal models of compulsive eating also interfere with drug administration.

- For more information, see <http://www.nimh.nih.gov/press/lightswitchneurons.cfm>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences* and Chapter 3: *Technology Development*.
- (E) (NIDA, NIMH)

The Scientific Basis of Acupuncture: Ongoing research on acupuncture includes a substantial portfolio of basic and translational studies employing state-of-the-art neuroimaging technology. This work is beginning to provide powerful scientific insight into the potential neurobiological mechanisms of action by which acupuncture might work. Clinical trials of acupuncture for a number of medical conditions are also under way, including studies examining (1) the potential role of traditional acupuncture as an additive/alternative treatment for the prevention of acute cardiac events in patients with coronary artery disease, (2) whether manual or electro-acupuncture contributes to neurological recovery after spinal cord injury, and (3) the efficacy of acupuncture in relieving post-thoracotomy pain syndrome (severe and persistent aching or burning pain along surgical scars in the chest).

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

Cochlear Implants: One of the more groundbreaking biomedical achievements in the last 30 years has been the cochlear implant, an electronic device that provides a sense of sound to individuals who are profoundly deaf or severely hard-of-hearing. Cochlear implants process sounds from the environment and directly stimulate the auditory nerve, bypassing damaged portions of the inner ear. Nearly 100,000 individuals worldwide have been fitted with cochlear implants. In the United States, approximately 22,000 adults and nearly 15,000 children have received them. Derived in part from NIH-funded research that dates back to the early 1970s and continues today, this remarkable technology has enabled deaf and severely hard-of-hearing individuals to enjoy an enhanced quality of life. NIH-supported scientists showed that profoundly deaf children who receive cochlear implants at an early age develop language skills at a rate comparable to that of children with normal hearing. They also found that the benefits of the cochlear implant in children far outweigh its costs. Scientists can now study the large groups of children who were identified early for hearing loss and use this knowledge to document how treatments such as cochlear implants can lead to improved speech and language acquisition, academic performance, and economic outcomes for these children.

- [Nicholas JG, Geers AE. *Ear Hear* 2006;27:286-98](#), PMID: 16672797
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*.

- (E) (NIDCD)

Neurobiology of Appetite Control: NIH supports research to elucidate the complex biologic pathways that converge in the brain to regulate appetite. Examples include research on how serotonin reduces appetite; the actions of the protein mTOR in sensing nutrients in the body so as to modulate food intake; and a strategy to block ghrelin, a stomach-secreted hormone that signals the brain to increase food intake. This research has implications for new therapies for obesity.

- [Cota D, et al. *Science* 2006;312:927-30.](#) PMID: 16690869
- [Heisler LK, et al. *Neuron* 2006;51:239-49,](#) PMID: 16846858
- [Zorrilla EP, et al. *Proc Natl Acad Sci U S A* 2006;103:13226-31,](#) PMID: 16891413
- For more information, see <http://tinyurl.com/22o9mv> (“Obesity” chapter)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NIDDK)

A Multidisciplinary Approach to Nicotine Addiction: Nicotine addiction is the number-one preventable public health threat and has enormous associated morbidity, mortality, and economic costs. NIH-supported research has generated new knowledge to support the development of more effective prevention messages and treatment approaches. Several notable examples characterize NIH’s multidisciplinary approach to targeting the best treatment (or combination of treatments) for nicotine addiction. Genomic studies have recently uncovered a series of genes that are associated with nicotine addiction and that could provide new targets for medications development and for the optimization of treatment selection. Pharmacologic studies, so critical to understanding the basis of nicotine’s mode of action, have recently revealed that its addictiveness may hinge upon its ability to slowly shut down or desensitize the brain’s response to nicotine. A recent imaging study indicated that a part of the brain called the insula may play an important role in regulating conscious craving. This exciting finding provides a new target for research into the neurobiology of drug craving and for the development of potentially more effective smoking cessation and other addiction treatments. Results of a Phase II clinical trial strongly suggest that a nicotine vaccine, which works by preventing nicotine from reaching the brain, may be a particularly useful tool for cessation programs in the not-too-distant future.

- For more information, see <http://www.drugabuse.gov/researchreports/nicotine/nicotine.html>
- This example also appears in Chapter 2: *Cancer*, Chapter 3: *Genomics*, and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDA, NCI) (GPRA Goal)

Treatments to Fight Methamphetamine Addiction: The abuse of methamphetamine—a potent and highly addictive psychostimulant—is a serious problem in the United States. Methamphetamine abuse can have devastating medical, psychological, and social consequences. Adverse health effects include memory loss, aggression, psychotic behavior, heart damage, and abnormal brain function. Methamphetamine abuse also contributes to increased transmission of hepatitis and HIV/AIDS and can spawn increased crime, unemployment, and other social ills. The good news is that methamphetamine abuse and addiction are treatable, and people do recover. As methamphetamine abuse has increased, so has NIH’s support of research to combat it, including research on genetics, brain development, and translation of findings. This research has led to the development of two effective behavioral therapies for methamphetamine addiction: (1) the Matrix Model, consisting of a 16-week program that includes group and individual therapy and addresses relapse prevention, behavioral changes, establishment of new drug-free environments, and other areas, and (2) Motivational Incentives for Enhanced Drug Abuse Recovery, a cost-effective incentive method for cocaine and methamphetamine addiction that has been shown to sustain abstinence in twice the number of participants engaged in treatment as usual. Increasingly,

community treatment providers nationwide are implementing motivational incentives as part of drug addiction treatment.

- For more information, see <http://www.drugabuse.gov/ResearchReports/Methamph/Methamph.html>
- For more information, see <http://www.drugabuse.gov/Testimony/6-28-06Testimony.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIDA)

Quantum Program: The NIH Quantum Grants Program has been developed to make a profound (quantum-level) advance in health care by funding research, over two phases, on targeted projects that will develop new technologies for the diagnosis, treatment, or prevention of a major disease or national public health problem. The first of the Quantum Grants was to engineer stem cell-based neurovascular regenerative units in a laboratory environment, which can then be implanted into the damaged cortex of stroke patients to provide a source of neural and vascular cells that will continue to develop and differentiate. This approach may lead to the first true treatment for stroke, which is one of the most common causes of disability and severely affects the quality of life of patients throughout the world. Another Phase I Quantum competition was completed in September 2007, with four additional grants awarded. The Phase II Quantum competition will begin in FY 2009.

- For more information, see <http://www.nibib.nih.gov/Research/QuantumGrants>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIBIB)

Prevention of Trauma-Related Mental Disorders in High-Risk Occupations: NIH is supporting a research initiative to develop and test preemptive interventions to prevent trauma-related disorders, such as posttraumatic stress disorder, among occupational groups at high risk for trauma exposure, such as the military, firefighters, police, and rescue workers.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-010.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIMH)

Traumatic Brain Injury Program: Traumatic brain injury (TBI) presents enormous challenges to neuroscience because of the numbers of people affected and the range of problems TBI can cause. The consequences of TBI may be subtle or severe, immediate or delayed, perhaps even predisposing to problems many years later in life. TBI can compromise virtually any human ability, depending on which parts of the brain are damaged. NIH supports a broad program of research, from studies of how TBI causes immediate and delayed damage to brain cells, to development of measurable diagnostic markers of damage, through large clinical trials to test interventions. NIH clinical studies are developing both emergency interventions to minimize damage and rehabilitation strategies to compensate for damage or encourage the brain to adapt. The high rate of TBI among military personnel in Afghanistan and Iraq presents a special concern. NIH intramural scientists are working with the Departments of Defense and Veterans Affairs to study the psychobiological consequences of TBI among military personnel, and NIH is working with all relevant Federal agencies to coordinate research activities on high-priority issues, including a 2006 interagency conference on TBI and follow-up meetings in 2007 and 2008 focusing on issues such as injury classification and potential combination therapies.

- (E/I) (NINDS, NICHD)

Epilepsy Research Benchmarks: In March 2000, NINDS convened a broad group of scientists, clinicians, people impacted by epilepsy, and public policymakers for a White House-initiated conference on the disorder. After this conference, NINDS developed a series of epilepsy research goals in three major topic areas: (1) interrupting and monitoring the development of epilepsy, (2) preventing epilepsy, and (3) developing more effective therapies. The Institute worked with the epilepsy research and patient communities to develop a series of benchmarks for tracking progress toward these goals. Researchers have made substantial progress since this meeting, and science has also evolved over this time. As a result, NINDS organized a session at the most recent Curing Epilepsy 2007 conference for the participants to discuss revisions to the first set of benchmarks. NINDS is currently collecting public feedback on these revised goals and will work with a group of representatives from the scientific community to refine the benchmarks for release at the 2007 American Epilepsy Society meeting.

- For more information, see <http://www.ninds.nih.gov/funding/research/epilepsyweb/index.htm>
- (E) (NINDS)

Neural Prosthesis Program: Neural prosthetic devices restore or supplement nervous system functions that have been lost through disease or injury, allowing people with disabilities to lead fuller and more productive lives. The NINDS Neural Prosthesis program pioneered the development of this technology beginning more than 35 years ago. The program has, directly or indirectly, catalyzed the development of cochlear implants for the hearing impaired, respiratory and hand grasp devices for people with spinal cord injuries, and deep brain stimulation for Parkinson's disease, among other contributions. Current work aims to restore standing and voluntary bowel and bladder control after spinal cord injury, to allow paralyzed persons to control devices directly from their brains, and to control seizures. Ongoing research also seeks to improve cochlear implants and to advance deep brain stimulation, which may be applicable to many brain disorders. Through the years, the program has fostered the development of a robust research community that now includes private-sector companies and represents a cooperative effort among several NIH Institutes, which coordinate their efforts with programs now under way in the Department of Veterans Affairs and the Department of Defense.

- For more information, see <http://www.ninds.nih.gov/funding/research/npp/index.htm>
- more information, see <http://www.nih.gov/about/researchresultsforthepublic/CochlearImplants.pdf>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation* and Chapter 3: *Technology Development*.
- (E) (NINDS, NCRR, NEI, NIBIB, NICHD, NIDCD)

Link Between Eye Movement and Reward: Dopamine is vital to motor behaviors, but neurons that release dopamine carry signals related to rewards, not body movements. As a solution to this puzzle, recent theories propose that the reward-related dopamine signals are used for learning of motor behaviors. However, it is unknown how dopamine neurons acquire the reward-related signals. NIH scientists have shown that a small brain area called the lateral habenula controls dopamine neurons by inhibiting them and thereby suppressing less rewarding eye movements. This discovery opens up new research connecting emotion and motivation to motor behaviors.

- [Matsumoto M, Hikosaka O. Nature 2007;447:1111-5](#), PMID: 17522629
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (I) (NEI)

Genes Involved in the Regulation of Sensitivity to Alcohol: Low doses of alcohol are stimulating in both humans and animals while higher doses have sedating effects. Sensitivity to alcohol, however, varies across individuals and low sensitivity to alcohol is a risk factor for the development of alcohol dependence in humans. Recent animal studies have identified several genes that alter sensitivity to alcohol and may provide targets for medications development.

- Researchers have discovered a genetic mutation that disrupts the function of the fruit fly gene RhoCAP18B, causing the flies to be much more resistant to alcohol sedation. Other variants of the same gene, each of which has a distinctly different effect on the response to alcohol, were subsequently identified.
- [Rothenfluh A, et al. *Cell* 2006;127:199-211](#), PMID: 17018286
- Another fruit fly gene, homer, has been shown to be required for normal sensitivity and tolerance to alcohol. This study shows that ethanol sensitivity and tolerance co-map to the same population of neurons, suggesting that the neuronal circuits controlling these two behaviors, known to contribute to alcohol dependence, are shared.
 - [Urizar NL, et al. *J Neuroscience* 2007;27:4541-51](#), PMID: 17460067
 - This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
 - (E) (NIAAA)

Increased Endocannabinoid Signaling Increases Ethanol Consumption and Decreases Acute Ethanol Intoxication: Endocannabinoids, the naturally occurring substances in the brain that act on the same receptors as the active ingredients of marijuana, have been discovered to play a role in regulating appetite for alcohol. NIH-supported scientists discovered that mice lacking expression of fatty acid amidohydrolase (FAAH), the main endocannabinoid-degrading enzyme, showed an increased appetite for ethanol, decreased sensitivity to ethanol-induced sedation, and faster recovery from ethanol-induced motor incoordination. These results show that impaired FAAH function leads to increased voluntary alcohol intake and point to FAAH both as a potential susceptibility factor and a therapeutic target for excessive alcohol consumption.

- [Hansson AC, et al. *Neuropsychopharmacol* 2007;32:117-26](#), PMID: 16482090
- [Blednov YA, et al. *Neuropsychopharmacol* 2007;32:1570-82](#), PMID: 17164820
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E/I) (NIAAA)

Re-innervation of Regenerated Hair Cells: Hair cells detect sound and are named for the hairlike projection from their top surface. Researchers hope one day to regenerate hair cells in the inner ears of people who have experienced damage due to noise, drugs, or disease. However, the ability to regrow hair cells will not restore hearing or balance without properly reconnected nerve endings. NIH-supported scientists used drugs to destroy hair cells and corresponding nerve endings in adult pigeons. (Unlike mammals, birds and other vertebrates are able to regenerate hair cells naturally.) Using a high-powered microscope, the scientists examined tissue sections and determined that the re-innervation process was similar to the pattern observed during normal nerve cell development. Although the regenerated nerve endings were less complex than those generated in normal development, many balance-related behaviors nevertheless fully recovered. This finding suggests that scientists may need only to regenerate simple nerve endings to restore the sense of balance. Further clarification of the mechanisms involved in nerve cell regeneration is essential for the potential recovery of balance and hearing in people with inner-ear damage.

- [Zakir M, Dickman JD. *J Neurosci* 2006;26:2881-93](#), PMID: 16540565

- (E) (NIDCD)

Neurodegeneration: Fighting the Effects of Age, Exposure, and Disease

Alzheimer's Disease Neuroimaging Initiative (ADNI): ADNI is an innovative public-private partnership for examining the potential for serial MRI, positron emission tomography (PET), or other biomarkers to measure earlier and with greater sensitivity the development and progression of mild cognitive impairment and Alzheimer's disease. Early results suggest that researchers may be able to reduce the costs associated with clinical trials by improving imaging and biomarker analysis. One ADNI study found that a standard model can be used to monitor the performance of MRI scanners at multiple clinical sites, ensuring the accuracy of the MRI images. In another study, investigators compared changes over time in PET scans of brain glucose metabolism in people with normal cognition, mild cognitive impairment, and Alzheimer's disease and found that scans correlated with symptoms of each condition and that images were consistent across sites. This finding suggests that PET scans may be a valid method for monitoring the effectiveness of therapies in future clinical trials. More than 200 researchers have already accessed a public database containing thousands of brain images and related clinical data obtained through blood and cerebrospinal fluid analyses.

- For more information, see <http://www.loni.ucla.edu/ADNI>
- For more information, see <http://www.nia.nih.gov/Alzheimers/ResearchInformation/ClinicalTrials/ADNI.htm>
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (NIA, NIBIB)

Genome-Wide Genotyping in Parkinson's Disease: NIH researchers recently conducted genome-wide genotyping of publicly available samples from a cohort of 267 patients with Parkinson's disease and 270 neurologically normal control subjects to identify any common genetic variability with significant effect on the risk for Parkinson's disease. The project has produced approximately 220 million data points in the 537 subjects, the largest collection of publicly available genotypes in a case-control cohort. The release of these data facilitates research on Parkinson's disease and other neurodegenerative disorders, and the genotypes from neurologically normal control subjects can be used as a comparison cohort for other studies, dramatically reducing the cost of future research.

- [Fung HC, et al. *Lancet Neurol* 2006;5:911-6](#), PMID: 17052657
- For more information, see <http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20060927parkinsons.htm>
- This example also appears in Chapter 3: *Genomics*.
- (E/I) (NIA, NINDS)

Ongoing Research on Complementary and Alternative Medical Approaches for Patients with Alzheimer's Disease or Dementia and Their Caregivers:

- A study in an animal model of Alzheimer's disease, evaluating whether fish oil, a safe and relatively inexpensive dietary supplement source of omega-3 fatty acids, shows similar or better effects than docosahexaenoic acid (DHA) in slowing the progression of changes associated with cognitive and functional decline in humans with Alzheimer's disease
- A feasibility study of polarity therapy as an intervention for family caregivers of people with dementia who experience high levels of stress and are at risk for physical and mental health illness
- Preclinical investigations of the potential activity and mechanisms of effect of (1) D-pinitol, a natural compound found in high concentrations in pine tree components and in smaller but significant concentrations in soy, and (2) substances derived from heat-processed ginseng and other related natural products.

- (E) (NCCAM)

Alzheimer’s Disease Cooperative Study (ADCS): Much of the NIH-supported clinical research on Alzheimer’s disease takes place through the ADCS. The study involves a consortium of centers in the United States and Canada where clinical trials are carried out on promising new therapies that may preempt the onset of Alzheimer’s disease or predict the disease’s development in vulnerable people. To date, approximately 4,600 people have participated in the trials. In FY 2007, new studies included a trial to demonstrate whether intravenous immunoglobulin is clinically useful for treating Alzheimer’s disease and a trial to examine whether treatment with docosahexaenoic acid, an omega-3 fatty acid, will slow cognitive decline in patients with Alzheimer’s disease.

- For more information, see <http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20061017ADCS.htm>
- For more information, see <http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/NeuroscienceOfAging/ProgramInitiatives/ADCS.htm>.
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIA)

Parkinson’s Disease Registry: NIEHS has begun to address the need for more precise data on the incidence and prevalence of Parkinson’s disease through support of a Parkinson’s disease registry in the State of California, where the large and diverse population, coupled with the wide range of exposures that exist through agriculture and other activities, provides a unique opportunity to investigate disease-environment links. The United States does not have a national health registry to supply data on Parkinson’s disease, so estimates are based on sampling by individual studies in specific locales. The Parkinson’s registry in California will allow us to base national estimates on a registry drawing upon a cross-section of the population in our most populous state.

- For more information, see <http://www.theipi.org/site/parkinson/section.php?id=101>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NIEHS)

Multiple Sclerosis: Although the exact cause of multiple sclerosis is unknown, research suggests a strong genetic component. NIH funds a number of studies to determine the underlying genetic causes of multiple sclerosis, including a project to identify regions of the genome containing multiple sclerosis susceptibility genes using a large familial dataset and genomic analysis tools. NIH also funds clinical trials to test therapies for multiple sclerosis, including the CombiRx trial, a randomized, controlled clinical trial comparing the efficacy of treatment combining beta-interferon and glatiramer acetate versus treatment with a single agent for relapsing forms of MS. A study conducted in conjunction with CombiRx by NIH intramural researchers (BioMS) is assessing multiple sclerosis biomarkers by using genomic and proteomic technology and relating the information obtained back to clinical and MRI data generated by the CombiRx clinical trial.

- [Gregory SG, et al. *Nat Genet* 2007;39:1083-91](#), PMID: 17660817
- [International Multiple Sclerosis Genetics Consortium, et al. *N Engl J Med* 2007;357:851-62](#), PMID: 17660530
- This example also appears in Chapter 2: *Autoimmune Diseases* and Chapter 3: *Clinical and Translational Research*.
- (E/I) (NINDS)

Age-Related Eye Disease Study, Part 2 (AREDS2): Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly in the United States and will be an increasing burden in future years, based on demographics. The original AREDS, which was completed in 2005, demonstrated that antioxidant vitamin and mineral supplements reduced the progression to advanced AMD by 25 percent. Building on these landmark findings, AREDS Part 2 (AREDS2) is assessing additional supplements (lutein, zeaxanthin, and long-chain omega-3

fatty acids) as a treatment for AMD and cataracts. AREDS2 is also evaluating effects of eliminating beta-carotene and/or reducing zinc in the original AREDS formulation on AMD progression. AREDS2 investigators will also explore gene-environment interactions in the development of these conditions, cognitive function, and cardiovascular health.

- For more information, see <http://www.areds2.org>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NEI, NIA)

Retinal Neurodegeneration Program: The Retinal Neurodegeneration Program is a new multidisciplinary intramural research program that combines basic, preclinical, and translational research to develop and test therapeutic interventions in several retinal degenerative diseases. These interventions include gene therapy, small molecules, neurotrophic factors, and cell-based systems, in combination with a variety of treatment delivery technologies.

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (I) (NEI)

Alzheimer's Disease Genetics Initiative and Data Storage: Only one of the four validated Alzheimer's disease genes, *APOE*, has been definitively linked with the more common late-onset form of the disease. A fifth gene, *SORL1*, has recently been linked with late-onset Alzheimer's disease in some studies. The goal of the Alzheimer's Disease Genetics Initiative is to develop the resources necessary for identifying the late-onset Alzheimer's disease risk factor genes and the interactions of genes with the environment. In FY 2006, NIH achieved its goal to recruit 1,000 families with two or more siblings living with Alzheimer's disease through an unprecedented alliance of Alzheimer's disease centers, researchers, and outreach with the Alzheimer's Association. To facilitate access by qualified investigators, all genetic data derived from NIH-funded studies on late-onset Alzheimer's disease genetics are deposited at a central data storage site at Washington University in St. Louis, another NIH-approved site, or both. Discovery of risk factor genes will help illuminate the underlying disease processes of Alzheimer's disease, open up novel areas of research, and identify new targets for drug therapy.

- For more information, see <http://www.niageneticsdata.org>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E/I) (NIA)

Understanding the Mechanisms of Alcohol-Induced Tissue Injury: Heavy alcohol use has an impact on nearly every organ system of the body (the most vulnerable being the brain and liver), and the resulting pathological conditions contribute to increased mortality and morbidity among all age and racial/ethnic groups and both sexes. NIH is especially interested in elucidating mechanisms of injury common to multiple body and organ systems. A number of Program Announcements and RFAs have been issued to support research to increase our understanding of the underlying cellular and molecular mechanisms of tissue injury caused by alcohol consumption, including alcohol's genetic, epigenetic, and metabolic effects. The long-term goals of these initiatives are to identify biomarkers for alcohol exposure and for the early detection of alcohol-induced tissue injury, as well as to develop new therapeutics that control or modify outcomes of chronic alcohol use.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-065.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-360.html>
- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-361.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-004.html>

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-AA-06-005.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 2: *Life Stages, Human Development, and Rehabilitation*, and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E/I) (NIAAA)

Cognitive and Emotional Health Project: The Healthy Brain: The purpose of this initiative is to assess the state of longitudinal and epidemiological research on determinants of cognitive and emotional health in aging adults. The project has completed a comprehensive review of measures that have been (or could be) used in epidemiological research. To help NIH learn what epidemiological data exist on the cognitive and emotional health of adults in the United States, the project polled investigators who are conducting these types of studies and created an online database. In addition, a Critical Evaluation Study Committee conducted an analysis and published a summary of the existing scientific literature pertaining to factors involved in the maintenance of cognitive and emotional health in adults. NIH is discussing new initiatives to expand this project, including promoting the use of existing datasets and developing ancillary studies to examine how cognitive and emotional health influence each other.

- For more information, see [http://www.alzheimersanddementia.com/article/S1552-5260\(05\)00503-0/abstract?articleId](http://www.alzheimersanddementia.com/article/S1552-5260(05)00503-0/abstract?articleId)
- For more information, see <http://trans.nih.gov/cehp>
- This example also appears in Chapter 3: *Epidemiological and Longitudinal Studies*.
- (E) (NINDS, NIA, NIMH)

Progress in Parkinson's Disease Research: For the past 7 years, NIH has been actively engaged in identifying gaps in Parkinson's disease research and developing programs to address them. Examples of progress include initiation of Phase III clinical trials of creatine and coenzyme Q10 to treat early Parkinson's disease; development of diagnostic criteria for depression and psychosis in people with Parkinson's disease; and support for a Parkinson's disease Gene Therapy Study Group. NIH has also begun to formally assess the effectiveness of its programs by completing an evaluation of its Morris K. Udall Centers of Excellence in Parkinson's Disease Research. This evaluation included an assessment of scientific progress made by the centers and the value of using a centers mechanism, as well as an exploration of the effectiveness of program management and review in supporting the centers. The Working Group tasked with this evaluation released its findings in September 2007.

- For more information, see <http://www.ninds.nih.gov/funding/research/parkinsonsweb/index.htm>
- For more information, see <http://www.parkinsontrial.ninds.nih.gov/index.htm>
- For more information, see http://www.ninds.nih.gov/news_and_events/press_releases/pressrelease_creatine_03222007.htm
- For more information, see http://www.ninds.nih.gov/udall_centers_evaluation
- (E) (NINDS)

Toward Better Treatment for Muscular Dystrophy: Activities funded by NIH are pursuing multiple pathways to therapeutic development for the muscular dystrophies. NIH funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers, designed to accelerate the translation of fundamental scientific advances to the clinic (see Chapter 4). NIH also recently funded two large-scale translational research projects in muscular dystrophy: one to develop small-molecule drugs for Duchenne and potentially other forms of muscular dystrophy and another to develop the optimal vector for vascular delivery of genes. A new NIH Government Performance and Results Act (GPRA) goal aims to advance two emerging strategies for treating muscular dystrophy to clinical trial readiness by 2013. The Muscular Dystrophy Coordinating Committee's *Action Plan for the Muscular Dystrophies* also identified therapy development goals to be pursued by NIH and the committee's partner agencies and organizations. A recent workshop convened by NIH reviewed the status of different therapeutic approaches for muscular dystrophy and discussed ways to move this research forward.

- For more information, see http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan.pdf
- For more information, see www.wellstonemdccenters.nih.gov
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (COE) (NINDS, NIAMS, NICHD) (GPRA Goal)

Translational Research on Alzheimer’s Disease: To move basic research on Alzheimer's disease and associated disorders into translational research and drug testing in clinical trials, this initiative includes drug discovery, preclinical development, and a program of toxicology services for academic and small business investigators who lack the resources to perform the required toxicology studies on promising therapeutic compounds. To closely monitor the progress of the translational projects, provide guidance, and foster interactions among investigators involved in translational research funded by these programs, NIH staff will hold the First Annual Investigators Meeting for Translational Research in September 2007.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PA-07-048.html>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E/I) (NIA)

Preclinical Efficacy of Ginkgo biloba in Alzheimer’s Disease: NIH-supported investigators recently published results showing that Ginkgo biloba, studied in an animal model of Alzheimer’s disease, reduces both the formation of the specific brain abnormalities seen in humans and the resulting paralysis seen in the animals. These experiments lend additional support to the hypothesis that Ginkgo biloba may be useful in slowing the progression of Alzheimer’s disease. That hypothesis is being tested in the largest clinical trial to date of Ginkgo biloba for the prevention of dementia, supported by NIH.

- [Wu Y, et al. J Neurosci 2006;26:13102-13](#), PMID: 17167099
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NCCAM)

Inflammatory Factor Mediates Nerve Degeneration in Glaucoma Model: In glaucoma, elevated eye pressure plays a role in damaging fibers in the optic nerve, which relays visual signals to the brain. However, the link between pressure and nerve damage is not well understood. Recent research in mice suggests a critical role for the protein tumor necrosis factor-alpha (TNF-a) in developing glaucoma. A molecular target in the glaucoma disease pathway opens up doors for drug therapy.

- [Nakazawa T, et al. J Neurosci 2006;26:12633-41](#)
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E) (NEI)

Gene Expression Changes in Facioscapulohumeral Muscular Dystrophy: Results from a genome-wide scan of skeletal muscle biopsies suggest a link between eye blood vessel defects and muscle defects that characterize facioscapulohumeral muscular dystrophy. Patient participants were recruited from the National Registry for Myotonic Dystrophy and patients with facioscapulohumeral muscular dystrophy and their family members.

- [Osborne RJ, et al. Neurology 2007; 68:569-77](#). PMID: 17151338
- For more information, see http://www.niams.nih.gov/Funding/Funded_Research/registries.asp#dystrophy
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems* and Chapter 3: *Genomics*.
- (E) (NIAMS, NCRR, NINDS)

Hereditary Hearing Loss: NIH recognizes that one of the most rapidly developing areas of research is functional genomics, which involves determining the identity, structure, and function of genes. Hereditary or genetic causes account for approximately 50-60 percent of the severe to profound cases of childhood hearing loss. NIH-supported scientists are working to understand the normal function of these genes and how they are altered in individuals with hereditary hearing loss. At present, more than 70 genes causing nonsyndromic hereditary hearing impairment have been mapped to intervals on particular chromosomes; many of these efforts were the result of collaborations involving NIH-supported scientists. In collaborative efforts with scientists in Colombia, India, Indonesia, Israel, Lebanon, Mexico, Newfoundland, Pakistan, Tunisia, Puerto Rico, and the United States, NIH is accelerating this gene discovery effort. These research investments to understand the genetic basis of communication disorders will help scientists develop diagnostic tests and better treatments for the millions of Americans with hereditary hearing impairment.

- [Morton CC, Nance WE. *N Engl J Med* 2006;354:2151-64](#), PMID: 16707752
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E/I) (NIDCD)

Advancing Neuroscience Research Through Collaboration

The NIH Blueprint for Neuroscience Research: The NIH Blueprint is a collaborative framework that brings together 16 NIH ICs and Offices that support neuroscience research. The Blueprint catalyzes research progress by developing tools, resources, and training opportunities that transcend the mission of any single NIH IC and serve the entire neuroscience community. In FY 2006, the Blueprint launched initiatives to develop new neuroimaging technologies, a clearinghouse to distribute and improve existing neuroimaging software, core resource centers, a neurological and behavioral assessment tool, and new genetically modified mouse models. The Blueprint also supported training programs in neuroimaging, computational neuroscience, and translational research. In FY 2007, the Blueprint released funding announcements to identify biomarkers for neurodegeneration, develop new ways to deliver therapeutics to the nervous system, and provide interdisciplinary training in neurodegeneration research.

- For more information, see <http://www.neuroscienceblueprint.nih.gov>
- This example also appears in Chapter 3: *Research Training and Career Development*.
- (E) (NINDS, NCCAM, NCCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

A Clearinghouse for Neuroimaging Informatics Tools and Resources: NIH understands that researchers seeking neuroimaging analysis software tools need a convenient way to find and compare useful software. Indeed, the best or most suitable neuroimaging analysis technologies for research may be hidden in someone's laboratory or some obscure corner of cyberspace. NIH is creating a Neuroimaging Informatics Tools and Resources Clearinghouse. The 14 NIH ICs that participate in the Neuroscience Blueprint have supported the development of sophisticated, high-quality neuroimaging informatics tools and resources. The clearinghouse is intended to facilitate the dissemination of those tools and resources and promote their adoption within the extended neuroimaging community. A contract has been awarded to create the clearinghouse infrastructure. The infrastructure will include a Web site that will not only provide access to tools and resources but will also provide ongoing opportunities for public comment to guide future development and enhancement of the tools. In addition to the contract award, grant awards are being made to individual extramural scientists to enable them to render their tools more suitable for this initiative. The awards will fund the enhancement of tools to make them easier to use, more broadly applicable, or more compatible with other existing tools. The clearinghouse was released to the public in October 2007.

- For more information, see <http://www.nitrc.org>

- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NIBIB, NCCAM, NCRR, NEI, NIA, NIAAA, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR, OBSSR)

NIMH Genetics Repository: Over the last 9 years, NIMH has built the infrastructure for large-scale genetics studies through the NIMH Human Genetics Initiative. Through this Initiative, NIMH established a repository of DNA, cell cultures, and clinical data that serve as a national resource for researchers studying the genetics of complex mental disorders.

- For more information, see <http://nimhgenetics.org>.
- This example also appears in Chapter 3: *Genomics* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E) (NIMH)

Practical Clinical Trials: NIH has completed primary and secondary phases of several practical clinical trials that have examined treatment effectiveness for mental disorders such as schizophrenia, bipolar disorder, and depression. The infrastructure developed for each of these large multisite trials—involving more than 10,000 participants at over 200 sites—has forged efficient, effective, and collaborative relationships between scientists and clinicians throughout the country. To capitalize on the national networks established for the trials, NIH will fund infrastructure-only support for the platform of clinical sites and an administrative core. It is anticipated that the platform will serve as a critical foundation for supporting participant enrollment, facilitating communication among trial sites, maintaining up-to-date training in diagnosis and treatment, and providing needed administrative organization.

- For more information, see <http://www.nimh.nih.gov/healthinformation/catie.cfm>
- For more information, see <http://www.nimh.nih.gov/healthinformation/stard.cfm>
- For more information, see <http://www.nimh.nih.gov/healthinformation/stepbd.cfm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NIMH)

NINDS Human Genetics Repository: In 2003, NINDS established the Human Genetics Repository to collect, store, characterize, and distribute DNA samples and cell lines and standardized clinical data for the research community. By June 2007, the repository held material from 16,683 subjects, including those with stroke (4,363), epilepsy (1,065), Parkinson’s disease (3,585), and motor neuron diseases such as ALS (2,445), as well as control samples (4,767). The ethnically diverse collection represents populations from the United States and several other countries. Investigators have submitted or published more than 50 scientific articles based on data from this resource, and technological advances allowing “whole genome screening” for disease genes have also enhanced its value.

- For more information, see <http://ccr.coriell.org/Sections/Collections/NINDS/?Sslid=10>
- This example also appears in Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E/I) (NINDS)

NIH Pain Consortium: The aims of the NIH Pain Consortium are to enhance pain research and promote collaboration among researchers across the many NIH ICs that have programs and activities addressing pain. The consortium held its second annual symposium, “Advances in Pain Research,” on May 1, 2007, to feature new and exciting advances in pain research and pain management. Topics included neuropathic pain, visceral pain, inflammatory pain, and treatment-induced pain. Participants included NIH and extramural scientific communities, health care providers, and the public. Consortium ICs also issue an NIH-wide Funding Opportunity Announcement,

“Mechanisms, Models, Measurement, and Management in Pain Research,” to encourage pain research and delineate cross-cutting NIH interests in pain.

- For more information, see <http://videocast.nih.gov/PastEvents.asp>
- For more information, see <http://painconsortium.nih.gov/index.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.
- (E/I) (NIDCR, CC, FIC, NCCAM, NCI, NCR, NIA, NIAAA, NIAMS, NIBIB, NICHD, NIDA, NIDCD, NIGMS, NIMH, NINDS, NINR, OBSSR, OD, ODP/ORD, ORWH, OTT)

Gene Expression Nervous System Atlas (GENSAT): Knowing where and when genes are active is a key to understanding how the nervous system develops, how the normal brain works, and what goes wrong in disease. More than half of all genes are active at some point in the brain, yet only a small fraction of these have been well characterized. To systematically address this issue, NIH initiated the GENSAT project. The project prescreens the activity of many genes at four developmental time points in several parts of the brain and spinal cord and, for genes of high interest, generates strains of mice in which a visible marker is turned on wherever and whenever the gene of interest is active. In addition to the value of the publicly accessible GENSAT database, the mice are useful for research on normal development and function and diseases. For example, researchers used GENSAT mice to discover that one of two previously indistinguishable types of nerve cells is selectively vulnerable in Parkinson’s disease. By revealing the molecular mechanism that kills the cells, these experiments also identified a new potential drug target. GENSAT is now a resource within the NIH Neuroscience Blueprint and will expand to include nerve cells in the eye, ear, and pain pathways.

- [Day M, et al. *Nat Neurosci* 2006;9:251-9](#), PMID: 16415865
- For more information, see <http://www.gensat.org/index.html>
- For more information, see <http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=search&db=gensat>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NINDS, NCCAM, NCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINR, OBSSR)

Programs to Accelerate Medications Development for Alcoholism Treatment: Alcoholism is a complex heterogeneous disease caused by the interaction between multiple genetic and environmental factors that differ from one drinker to another. Therefore a diverse repertoire of medications is needed to provide effective therapy to a broad spectrum of alcohol-dependent individuals. Although promising compounds have been identified, developing medications is a long and costly process with a low probability of success for any single agent. NIH has initiated collaborations with the pharmaceutical industry to ensure their interest in taking promising compounds through the final phase of clinical trials and subsequent FDA consideration. As part of this approach, two new programs have been initiated:

- Laboratories have been established to screen promising compounds with animal models, enabling faster determination of those that merit advancement to large, multisite studies. Animal studies have already produced several targets for human studies that are now under way, such as rimonabant, a cannabinoid CB1 receptor blocker, and antalarmin, a corticotropin-releasing factor receptor blocker.
 - A network of sites is being developed to conduct early Phase II proof-of-concept human trials. NIH will encourage the pharmaceutical industry to screen proprietary compounds in the preclinical models and, when results are positive, test them in the early human trials network.
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
 - (E/I) (NIAAA) (GPRA Goal)

The Collaborative Study on the Genetics of Alcoholism (COGA): In its 18th year, COGA is a multisite, multidisciplinary family study with the overall goal of identifying and characterizing genes that contribute to the risk for alcohol dependence and related phenotypes. COGA investigators have collected data from more than 300 extended families (consisting of more than 3,000 individuals) who are densely affected by alcoholism. Investigators have identified several genes, including *GABRA2*, *ADH4*, *ADH5*, and *CHRM2*, that influence the risk for alcoholism and related behaviors, such as anxiety, depression, and other drug dependence. In addition to genetic data, extensive clinical neuropsychological, electrophysiological, and biochemical data have been collected, and a repository of immortalized cell lines from these individuals has been established to serve as a permanent source of DNA for genetic studies. These data and biomaterials are distributed to qualified investigators in the greater scientific community to accelerate the identification of genes that influence vulnerability to alcoholism. COGA will continue to identify genes and variations within the genes that are associated with an increased risk for alcohol dependence and will perform functional studies of the identified genes to examine the mechanisms by which the identified genetic variations influence risk.

- For more information, see <http://zork.wustl.edu/niaaa>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Genomics*, and Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIAAA) (GPRA Goal)

Brain Disorders in the Developing World: Research Across the Lifespan: Brain disorders are the leading contributor to years lived with disability in all regions of the world, with the exception of sub-Saharan Africa. This program boosts research in the developing world on childhood disorders such as cerebral palsy and epilepsy, on mental illnesses such as depression and schizophrenia, and on degenerative disorders, such as stroke and Alzheimer's disease. Under this program, U.S. investigators and their foreign collaborators are studying the neurocognitive consequences of HIV/AIDS, the relationship between zinc nutrition and brain development, and the neurological disorders stemming from treatable infectious causes, such as cerebral malaria, cisticercosis, tuberculosis (TB), and bacterial sepsis.

- For more information, see http://www.fic.nih.gov/programs/research_grants/brain_disorder
- This example also appears in Chapter 2: *Life Stages, Human Development, and Rehabilitation*.
- (E) (FIC, NEI, NIA, NIAAA, NICHD, NIDA, NIEHS, NIMH, NINDS, ODS)

Trans-NIH Chronic Fatigue Syndrome Research: NIH coordinates chronic fatigue syndrome research through a trans-NIH Working Group on Research on Chronic Fatigue. This working group developed an action plan to enhance the status of chronic fatigue syndrome research at the NIH and among the external and intramural scientific communities. The working group held a workshop on grantsmanship in FY 2007 to provide researchers with an overview of funding opportunities, an understanding of the NIH funding process, and an opportunity to meet with program officials. In addition, the Office of Research on Women's Health and a subset of the working group ICs issued an RFA in FY 2006 to explicate how the brain, as the mediator of the various body systems involved, fits into the schema for understanding chronic fatigue syndrome. This RFA solicited proposals from multidisciplinary teams of scientists to develop an interdisciplinary approach to the study of chronic fatigue syndrome in men and women across the lifespan and resulted in seven new research projects on chronic fatigue syndrome.

- For more information, see <http://orwh.od.nih.gov/cfs.html>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html>
- For more information, see <http://orwh.od.nih.gov/cfs/2006NIHfundedCFSstudies.html>
- For more information, see <http://orwh.od.nih.gov/cfs/cfsFundingGMWs.html>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*.

- (E) (ORWH, NIAID, NIAMS, NIAAA, NIA, NICHD, NIDA, NIDDK, NINDS, NCRR, CSR, NIEHS, NIDCR, NINR, NHLBI, NIMH, NCCAM, FIC, ODS, OBSSR)

Mechanisms of HIV Neuropathogenesis: Domestic and Global Issues: Neurological manifestations, including HIV dementia and opportunistic infections and tumors, are among the most threatening complications of HIV infection. Emerging data indicate that the prevalence of HIV-related neurological disease differs across regions of the world, suggesting that different subtypes of HIV may be more or less capable of causing neuropathology, or that genetic variance among people in various regions of the world could affect susceptibility to HIV's neuropathological effects. NIH sponsored a meeting in the spring of 2007 to address these issues, resulting in the release of a funding announcement.

- For more information, see <http://synapse.neurology.unc.edu/venice>
- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-030.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NIMH, NINDS, OAR)

National NeuroAIDS Tissue Consortium (NNTC): The NNTC is a repository of brain tissue and fluids from highly characterized HIV-positive individuals. Established as a resource for the research community, NNTC includes information from more than 2,000 individuals, including approximately 641 brains, thousands of plasma and cerebrospinal fluid samples, and additional organs and nerves of interest.

- For more information, see <http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-08-021.html>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense* and Chapter 3: *Disease Registries, Databases, and Biomedical Information Systems*.
- (E/I) (NIMH, NINDS)

NIH Countermeasures Against Chemical Threats (CounterACT) Research Network: CounterACT Research Network, as reflected in an NIH GPRA goal, develops medical countermeasures to prevent, diagnose, and treat conditions caused by chemical agents that might be used in a terrorist attack or released by industrial accidents or natural disaster. The network, which has collaborated with the U.S. Department of Defense (DoD) from its inception in 2006, includes Research Centers of Excellence, individual research projects, small business research grants, contracts, and other programs that conduct basic, translational, and clinical research. One promising countermeasure, midazolam, which DoD researchers identified as a potential countermeasure against chemical agent-induced seizures, is entering clinical trials in epilepsy patients through the NINDS Neurological Emergency Clinical Trials Network, and NIH is collaborating with DoD to complete animal studies necessary for its FDA approval as a nerve agent treatment.

- For more information, see <http://www.ninds.nih.gov/funding/research/counterterrorism/index.htm>
- This example also appears in Chapter 2: *Infectious Diseases and Biodefense*.
- (E) (NINDS, NEI, NIAID, NIAMS, NIEHS, NIGMS)

Specialized Program of Translational Research in Acute Stroke (SPOTRIAS): The objective of SPOTRIAS is to serve as an incubator for translational and early-phase clinical research studies. SPOTRIAS sites are located at medical centers where staff have the capacity to evaluate and treat stroke patients very rapidly after symptom onset. NIH supports seven SPOTRIAS sites, which have made substantial progress, including impressive increases in the use of the "clot buster" tPA (tissue plasminogen activator) to treat acute stroke; the establishment of three interlinked repositories for protein and DNA tissue samples, neuroimages, and clinical data; enrollment of more than 640 individuals with acute stroke into treatment protocols; the management of 17 early-phase clinical trials; and the training of 25 research fellows.

- For more information, see <http://www.spotrias.com>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E/I) (NINDS)

The SMA Project: A decade ago, spinal muscular atrophy (SMA) was one of hundreds of poorly understood inherited disorders that affect the nervous system, and the outlook for developing treatments was bleak. The discovery of the gene defect that causes SMA dramatically improved prospects, revealing a rational strategy to develop drugs. The SMA Project is a novel approach to preclinical drug development and may serve as a model for other disorders. The project has brought together expertise from industry, academia, the FDA, and NIH to generate a detailed drug development plan. A “virtual pharma organization” develops and applies the resources to carry out the plan through subcontracts to companies that serve the pharmaceutical industry. The project created a new drug through extensive modification of indoprofen, a drug with known activity in experimental settings that was not suitable for clinical application. Through repeated modification and evaluation cycles in laboratory tests, the project produced hundreds of chemical compounds related to indoprofen and has made encouraging progress. In 2007, preclinical studies began to evaluate the two best candidates for clinical readiness. The best of these will likely be ready for early stage clinical testing in 2008 or 2009. In early 2008, the project also began two new drug development projects that could yield additional drug candidates for SMA.

- For more information, see <http://www.smaproject.org>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NINDS)

The NIH Toolbox for Assessment of Neurological and Behavioral Function: The NIH Blueprint for Neuroscience Research supports this contract awarded to the Evanston Northwestern Healthcare Research Institute. The project entails the development of a set of standardized neurological and behavioral measures of cognition, emotion, sensation, and motor function. The toolbox will foster uniformity among the basic measures used and allow comparisons or data compilations across multiple studies. This innovative approach to measurement will be responsive to the needs of researchers in a variety of settings and will place particular emphasis on measuring outcomes in clinical trials and functional status in large cohort studies, such as epidemiological and longitudinal studies.

- For more information, see <http://grants.nih.gov/grants/guide/notice-files/NOT-AG-06-008.html>
- For more information, see <http://www.enh.org/aboutus/press/article.aspx?id=4358>.
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (OBSSR, NCCAM, NCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, NIMH, NINDS, NINR)

The NIH Rapid Access to Intervention Development (RAID) Pilot Program: The NIH- RAID Pilot program makes available, on a competitive basis and at no cost to investigators, certain critical resources needed to develop new small-molecule drugs, including not only laboratory services but also expertise in the regulatory process. The program directly addresses roadblocks to moving research findings from bench to bedside. Among the projects approved are drugs for hepatic fibrosis, the blood diseases beta-thalassemia and sickle cell anemia, brain tumors, and the neurological disorders Friedreich’s ataxia and Alzheimer’s disease. The NIH-RAID Pilot program is part of the NIH Roadmap for Medical Research.

- For more information, see <http://nihroadmap.nih.gov/raid/index.aspx>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (Roadmap—all ICs participate)

Gene Influences Antidepressant Response: Whether depressed patients will respond to an antidepressant

depends, in part, on which version of a gene they inherit. In an NIH-supported study, investigators found that having two copies of one version of a gene that codes for a component of the brain's mood-regulating system increased the odds of a favorable response to an antidepressant by up to 18 percent, compared to having two copies of the other, more common version.

- For more information, see <http://www.nimh.nih.gov/press/stardgene.cfm>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Genomics*
- (E) (NIMH)

Genetic Roots of Bipolar Disorder Revealed by First Genome-Wide Study of Illness: According to NIH-funded research, the likelihood of developing bipolar disorder depends in part on the combination of small effects of variations in many different genes in the brain, none of which is powerful enough to cause the disease by itself.

- For more information, see <http://www.nimh.nih.gov/press/mcmahon-bipolar-genetics.cfm>
- This example also appears in Chapter 3: *Genomics*.
- (E) (NIMH)

Other Notable Activities

Advances in Treatment Development: NIH continues to fund research into the development of new, targeted medications and treatments for mental disorders.

- *Drug Development for Cognitive Impairments in Schizophrenia:* The Treatment Unit for Research on Neurocognition in Schizophrenia program is a network that is testing the safety and efficacy of new therapeutic compounds for treating the cognitive deficits of schizophrenia.
 - (E) (NIMH)
- *Studies of Fragile X Syndrome:* NIH has entered into a public-private partnership to study and test possible medications for treating fragile X syndrome, the most common cause of inherited mental impairment. Fragile X syndrome is caused by a single gene mutation that ultimately results in exaggerated activity of a brain protein called mGluR5. Researchers will study, in animals, the safety of chemical compounds known to block this mGluR5 activity. If this phase goes well, researchers will move forward with clinical studies.
 - (E) (NIMH, NINDS, NICHD)
- *Faster-acting depression treatments:* A recent NIH-funded study found that people with treatment-resistant depression experienced relief in as little as 2 hours after a single intravenous dose of ketamine, a medication usually used in higher doses as an anesthetic. Used in very low doses, ketamine is important for depression research but at higher doses could have side effects that may limit its clinical use. Nevertheless, this research could inform the development of faster and longer acting medications for treating depression.
 - For more information, see <http://www.nimh.nih.gov/press/ketamine.cfm>
 - This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
 - (I) (NIMH)

Clinical Research and Trials in Neurological Disease: NINDS provides extramural funding for more than 1,000 clinical research studies. Nearly 1 million people participate in these projects, and it is essential to assess the return on this investment in improving quality of life. NINDS contracted an independent evaluation of the costs and benefits of its Phase III clinical trials. Investigators found that, although the total cost of clinical trials in the study was \$335 million, the cumulative benefits over a 10-year period exceeded \$15 billion and added 470,000 healthy years of life to people in the United States. NINDS is extending this evaluation approach by developing a computer model that will estimate the public health impact of any given clinical trial in neurology or neurosurgery. This model will be publicly available for use by researchers and the Institute to facilitate decision-making. NINDS is also assessing ways to further improve its trials. To this end, the Institute has funded a Neurological Emergencies Treatment Trials (NETT) Network to facilitate high-quality clinical trials in acute neurological disorders and accelerate the implementation of new therapies into practice in emergency departments.

- [Johnston SC, et al. *Lancet* 2006;367:1319-27](#), PMID: 16631910
- For more information, see <http://www.nett.umich.edu/nett/welcome>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NINDS)

Scientific Basis of the Placebo Effect: The placebo effect can be defined as the measurable, observable, or felt changes that occur during, but are not directly attributable to, a specific health intervention. It is a ubiquitous and frequently powerful phenomenon that operates in all forms of medicine, so good clinical research is designed to account for its effects as well as those of the intervention under study. Because of the power of the placebo effect, it is equally important to understand the mechanisms by which it operates and to explore how its benefits might be maximized to enhance the quality and effectiveness of all forms of health care. An ongoing NIH initiative is examining multiple aspects of the placebo effect through interdisciplinary investigations employing molecular, physiological, biochemical, immunological, genetic, behavioral, and social science approaches. This work is beginning to shed light on many facets of the placebo effect. For example, one recently published study showed that placebo-associated pain relief was correlated with activation of areas of the brain that are associated with pain relief that occurs through both innate mechanisms and with use of opioid narcotics. Other ongoing studies are examining the role and importance of the placebo effect in the relationship between patient and health care provider.

- [Zubieta JK, et al. *J Neurosci* 2005;25:7754-62](#), PMID: 16120776
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

Reducing Disparities in Stroke: NIH is actively engaged in a number of research projects designed to identify risk factors for stroke in minority populations and enhance prevention and treatment in these groups. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is an observational study to explore the role of race and geographic differences on the prevalence of risk factors for stroke and on stroke incidence and mortality. To date, researchers have recruited approximately 27,000 of a projected 30,000 individuals (about 50 percent African American and 50 percent White) and have already published a number of important findings on their baseline data. NIH has also established an acute stroke research and care center at the Washington Hospital Center, a community hospital in Washington, DC, where more than 75 percent of stroke patients are African American or Hispanic. The center will collect data to aid in stroke prevention programs and will run two clinical trials, one on secondary stroke prevention and another on increasing the use of tissue plasminogen activator among minorities. The program directly addresses GPRA Goal SRO-8.9.2: "By 2018, identify culturally appropriate, effective stroke prevention/intervention programs in minority communities."

- For more information, see <http://www.regardsstudy.org/index.htm>
- This example also appears in Chapter 2: *Minority Health and Health isparities*.
- (E/I) (NINDS)

Blending Initiative: Bench to Bedside to Community: Efforts to systematically move science-based interventions and practices into community settings are exemplified in the testing of drug abuse treatment approaches in the community settings where they will be used by drug treatment professionals who are trained to implement them. This work is occurring through the National Drug Abuse Treatment Clinical Trials Network at NIH, which involves practitioners from community treatment programs in formulating research protocols and provides real-world feedback on their success and feasibility. The adoption of the addiction medication buprenorphine by a growing number of community treatment programs that treat patients with opioid addiction is an example of real culture change issuing from NIH clinical research. A similar approach is under way to enhance treatment for drug-addicted individuals involved with the criminal justice system through research supported under the Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) initiative. CJ-DATS seeks to achieve better integration of drug abuse treatment for criminal offenders with other public health and public safety forums and is a collaborative effort by NIH and multiple Federal agencies and health and social service professionals. These initiatives are helping to change the culture of how drug abuse treatment is delivered in this country.

- For more information, see <http://www.drugabuse.gov/CTN>
- For more information, see <http://www.cjdats.org>
- For more information, see <http://www.drugabuse.gov/Blending>
- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems*, Chapter 3: *Clinical and Translational Research*, and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E) (NIDA) (GPRA Goal)

Hearing Aids and Directional Microphones: Approximately 32.5 million American adults report some degree of hearing loss, according to data from the National Center for Health Statistics 2003 National Health Interview Survey. Although almost 95 percent of Americans with hearing loss could have their hearing treated with hearing aids, only about 20 percent of Americans with hearing loss have hearing aids, and many who wear them are dissatisfied with them. Hearing in noisy environments is a major unsolved problem faced by hearing aid users, and of all available technologies, directional microphones currently show the most promise for addressing this problem. NIH-supported scientists have been studying the tiny fly *Ormia ochracea*, which has such sensitive directional hearing that it has inspired ideas for a new generation of hearing aids. The fly's ear structure, which permits ultrasensitive time coding and localization of sound, provides a model for scientists and engineers in developing new miniature directional microphones for hearing aids that can focus sound amplification on speech. To improve hearing aid technology so that users can better understand speech in a noisy background, NIH-supported scientists successfully completed a prototype of a low-power, highly directional microphone small enough to fit into a hearing aid. The use of improved directional microphones in hearing aids will improve the quality of life for individuals with hearing loss who depend on hearing aids to understand spoken language.

- [Miles RN, Hoy RR. *Audiol Neurotol* 2006;11:86-94](#), PMID: 16439831
- This example also appears in Chapter 3: *Technology Development*.
- (E) (NIDCD) (GPRA Goal)

Visual Processing in Neuroscience Blueprint: Much of the cerebral cortex of the brain is devoted to processing the images that flood our eyes. The visual cortex also connects with many regions of the brain that govern memory, language, movement, and a myriad of other cognitive abilities. NIH's visual processing research portfolio prioritizes understanding of how the brain processes visual information, how brain activity results in visual perception, and how the visual system interacts with other cognitive systems.

- For more information, see <http://www.neuroscienceblueprint.nih.gov>
- For more information, see www.nei.nih.gov/funding/app.asp
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NEI)

Centers on Suicide Prevention: In response to the 2002 Institute of Medicine Report “Reducing Suicide: A National Imperative,” NIH issued an RFA and funded three centers focused on suicide intervention and prevention. Now in their third year of support, the centers have conducted pilot intervention studies with patients suffering from mental and substance use disorders.

- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NIMH, NIAAA, NIDA)

Understanding How Prefrontal Cortex Affects Cognitive Function: In FY 2008, NIH will support an RFA to stimulate research on how a brain region called the prefrontal cortex interacts with other parts of the brain to give rise to sophisticated behavior and cognitive function. Abnormal functioning of the prefrontal cortex is associated with mental disorders such as schizophrenia and depression.

- For more information, see <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-110.html>
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIMH)

Brain Tumor: The NIH Brain Tumor Progress Review Group identified many priorities for the field. Research on understanding and preventing brain tumor dispersal was one of the group’s highest scientific priorities, and NIH funds a number of projects in this area, many of which were submitted in response to a Program Announcement with set-aside funds issued in 2004. NIH also funds clinical studies investigating therapy delivery to the brain and evaluating the safety and tolerability of various therapies, including immunological therapies, vaccine therapy, monoclonal antibodies, and combination therapies. The Surgical and Molecular Neuro-Oncology Unit within the NIH Division of Intramural Research investigates basic mechanisms of brain tumor development and chemotherapy resistance to find new therapeutic strategies, particularly for malignant gliomas.

- For more information, see http://www.ninds.nih.gov/find_people/groups/brain_tumor_prg/index.htm
- This example also appears in Chapter 2: *Cancer*.
- (E/I) (NINDS, NCI)

Know Stroke in the Community Educational Campaign: In 2004, NIH entered a first-time partnership with CDC to launch a new grassroots education program called Know Stroke in the Community. The program was designed to identify and enlist the aid of community leaders, called “Stroke Champions,” who worked to educate communities about the signs and symptoms of stroke. The program focuses on reaching African Americans, Hispanics, and seniors in communities that have the health care systems in place to treat stroke. In 2005-2006, the program had been implemented in 11 cities, educating 168 Stroke Champions who have conducted more than 600 community events.

- This example also appears in Chapter 2: *Minority Health and Health Disparities* and Chapter 3: *Health Communication and Information Campaigns and Clearinghouses*.
- (E/I) (NINDS)

Peripheral Neuropathies: NIH funds studies focused on understanding the genetic basis and molecular and cellular mechanisms of many peripheral neuropathies, including diabetic neuropathy, HIV/AIDS-related and other infectious neuropathies, inherited neuropathies such as Charcot-Marie-Tooth, inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy, and rare forms of peripheral neuropathy. In October 2006, NIH held a workshop that looked across different peripheral neuropathies to focus on steps needed for therapy development. The workshop brought together researchers in inherited and acquired peripheral neuropathies, representatives from voluntary disease groups, and NIH staff.

- (E) (NINDS, NIDDK)

Rare Disorders: NIH supports research to uncover the causes of and develop treatments for the hundreds of rare disorders that affect the nervous system while also promoting research on topics such as stem cells, gene therapy, and neuroimaging that will impact multiple rare disorders. New NIH-funded grants in FY 2006 and 2007 focused on rare diseases, such as Friedreich's ataxia, ALS, transmissible spongiform encephalopathies, and Rett syndrome. NINDS also collaborates with the Office of Rare Diseases (ORD) and patient voluntary organizations to stimulate research via workshops or grant solicitations. For example, lysosomal storage disorders, such as Fabry, Niemann-Pick, and Gaucher diseases, are rare genetic diseases with neurological manifestations. NINDS, ORD, and a patient voluntary group cosponsor an initiative to spur new research on the delivery of therapies for lysosomal storage disorders across the blood-brain barrier.

- For more information, see <http://grants.nih.gov/grants/guide/pa-files/PAS-06-202.html>
- For more information, see http://www.ninds.nih.gov/about_ninds/plans/a-t_plan.htm
- (E) (NINDS, NCI, NCR, NEI, NHGRI, NHLBI, NIA, NIAID, NICHD, NIDDK, NIEHS, NIGMS, ODP/ORD)

Translational Research: To meet the special needs of translational research across neurological disorders, NINDS has developed a program to support pilot projects, full-scale collaborative teams in academia and small businesses, and training efforts. Investigator-initiated proposals are rigorously peer reviewed, and expertise and criteria are tailored to translational research objectives. Funding is milestone driven, and the program fosters collaborative research. Ongoing projects are developing drug, stem cell, or gene therapies for ALS, Batten disease, epilepsy, Huntington's disease, Duchenne and other muscular dystrophies, Parkinson's disease, tuberous sclerosis, and stroke and other disorders. In 2008 the program will expand to include molecular diagnostics, which are critical for catching disease early, when intervention is most likely to succeed.

- For more information, see <http://www.ninds.nih.gov/funding/research/translational/index.htm>
- This example also appears in Chapter 3: *Clinical and Translational Research*.
- (E) (NINDS)

Acupuncture for Osteoarthritis of the Knee: Clinical trials supported by NIH and others suggest that acupuncture may have a useful role in treating a variety of chronic painful conditions, hypertension, and obesity. For example, in 2006 NIH-funded investigators reported findings from the longest, largest, randomized, controlled clinical trial of acupuncture ever conducted. The results demonstrated that acupuncture is an effective adjunct to conventional treatment for osteoarthritis, the most common form of arthritis and a major cause of pain, limitation of activity, and health care utilization among the elderly. Study participants receiving acupuncture had significantly reduced disability and improved quality of life. The innovative trial design resulted from an interdisciplinary collaboration of rheumatologists, licensed acupuncturists, and biostatisticians, ensuring that the research methodology was scientifically sound and accurately reflected acupuncture as traditionally practiced.

- [Manheimer E, et al. *Acupunct Med* 2006;24:S7-14](#), PMID: 17308513

- This example also appears in Chapter 2: *Chronic Diseases and Organ Systems* and Chapter 3: *Clinical and Translational Research*.
- (E) (NCCAM)

How We Detect Taste at the Molecular Level: Taste is critical for discriminating between nutritious and spoiled foods. Taste disorders can lead to reduced appetite and poor nutrition. Scientists are trying to increase their understanding by identifying proteins that we produce to help detect taste. Taste cells are clustered in taste buds on the tongue and palate. NIH-supported scientists have identified a new protein, PKD1L3, found specifically in taste cells. The PKD1L3 protein forms a channel that allows tastants, such as sodium ions or protons, to enter through taste cell membranes so that tastes can be detected. Another group of NIH-supported scientists determined that the protein is located in taste pores and is activated by acids (sour) but not other tastants. A third group of NIH-supported scientists reports that mice lacking PKD2L1-expressing cells cannot detect sour tastants, but can detect all others. Together, these three reports suggest that PKD1L3 channels detect sour tastants in food. Scientists can now explain how humans detect the flavors sweet, sour, bitter, and umami, or savory, at the cellular level. This advance in understanding taste may help scientists treat taste impairments and could also lead to the development of better salt and sugar substitutes for the millions of Americans on restricted diets to control high blood pressure, diabetes, and obesity.

- [Lopez-Jimenez ND, et al. *J Neurochem* 2006;98:68-77](#), PMID: 16891422
- [Huang AL, et al. *Nature* 2006;442:934-8](#), PMID: 16929298
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E/I) (NIDCD)

Stuttering: Stuttering is a communication disorder with notable physical and emotional challenges to the speaker and sometimes to the listener. It is estimated that approximately 3 million Americans stutter. Stuttering affects individuals of all ages but occurs most frequently in young children between the ages of 2 and 6 who are developing speech and language. Boys are three times more likely to stutter than girls. Most children, however, outgrow their stuttering. It is estimated that less than 1 percent of adults stutter. NIH-supported scientists identified a specific location for a gene on chromosome 12 that seems to be an important contributor to stuttering in a series of 40 highly inbred families of Pakistani origin. Determining the underlying molecular causes of stuttering may lead to improved diagnosis and treatment.

- [Riaz N, et al. *Am J Hum Genet* 2005;76:647-51](#), PMID: 15714404
- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (E) (NIDCD)

Discovering the Molecular Mechanisms of Pain: Nociception, the sensory component of pain, depends in part on the intricate network of sensory transmission within our bodies, stretching from our extremities to the spinal cord and onward to the brain. But on its most fundamental level, nociception involves molecules and chemical mechanisms. NIH scientists have reported progress in understanding precisely how individual molecules in our nerve cells generate, transmit, and sustain sensory signals. They discovered that a much-studied protein called cyclin-dependent kinase 5 (Cdk5) plays a regulatory role in pain signaling between sensory nerves in the spinal cord and nerve ganglia. Their results offer the first direct evidence of this regulatory role for Cdk5. The authors also reported the first evidence from animal studies of the importance of Cdk5 activity in inflammation. These findings point the way for additional research, suggesting that new analgesic drugs that alter Cdk5 activity one day may be beneficial in treating pain.

- [Pareek TK, Kulkarni AB. *Cell Cycle* 2006;5:585-8](#), PMID: 16552189
- [Pareek TK, et al. *Proc Natl Acad Sci U S A* 2006;103:791-6](#), PMID: 16407116

- This example also appears in Chapter 3: *Molecular Biology and Basic Sciences*.
- (I) (NIDCR)

DNA Test for Charcot-Marie-Tooth Disease: Charcot-Marie-Tooth disease, one of the most common inherited neurological disorders, affects 1 in 2,500 people in the United States. Its symptoms start in early adulthood and include progressive arm and leg pain that leads to difficulty walking and manipulating objects. Using a special strain of mice, new genomic technologies, and information from the mouse and human genome sequences, NIH-funded researchers rapidly identified a mutation that causes a subtype of the disease. Knowledge of the specific gene defect will enable development of a DNA test to confirm the diagnosis in patients and predict risk for family members.

- [Chow CY, et al. *Nature* 2007;448:68-72](#), PMID: 17572665
- For more information, see <http://www.med.umich.edu/opm/newspage/2007/charcot.htm>.
- This example also appears in Chapter 3: *Genomics*.
- (E) (NIGMS, NINDS)

NIH Strategic Plans Pertaining to Neuroscience and Disorders of the Nervous System

National Institute of Neurological Disorders and Stroke (NINDS)

- [Neuroscience at the New Millennium](#)
- [Benchmarks for Epilepsy Research](#)
- [Report of the Stroke Progress Review Group](#)

National Eye Institute (NEI)

- [National Plan for Eye and Vision Research](#) (2004)
- [Vision Research—A National Plan 1999-2003: A Report of the National Eye Advisory Council](#)
- [Progress in Eye and Vision Research 1999-2006](#)
- [Ocular Epidemiology Strategic Planning Panel Report—Epidemiological Research: From Populations Through Interventions to Translation](#) (2007)
- [Age-Related Macular Degeneration Phenotype Consensus Meeting Report](#)
- [Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration Workshop Report](#)

National Institute on Aging (NIA)

- [Living Long and Well in the 21st Century: Strategic Directions for Research on Aging](#)

National Institute on Deafness and Other Communication Disorders (NIDCD)

- [FY 2006-FY 2008 NIDCD Strategic Plan](#)

National Institute of Mental Health (NIMH)

- [NIMH Strategic Plans and Priorities](#)
- [Breaking Ground, Breaking Through: The Strategic Plan for Mood Disorders Research](#)

- [Pathways to Health: Charting the Science of Brain, Mind, and Behavior](#)

National Institute on Drug Abuse (NIDA)

- [NIDA Draft Strategic Plan](#)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

- [National Institute on Alcohol Abuse and Alcoholism Five Year Strategic Plan FY 08-13](#)
- [Mechanisms of Alcohol Addiction](#)

National Center for Complementary and Alternative Medicine (NCCAM)

- [Expanding Horizons of Health Care: Strategic Plan 2005-2009](#)

Unice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

- [Neuroscience research at NICHD](#)
- Branch Reports to Council with Future Research Directions:
 - National Center for Medical Rehabilitation Research NICHD, Report to the National Advisory Child Health and Human Development (NACHHD) Council, January 2006
 - [National Center for Medical Rehabilitation Research \(NCMRR\), NICHD, Report to the NACHHD Council, January 2006](#)
 - [Developmental Biology, Genetics, and Teratology Branch, Report to the NACHHD Council, September 2006](#)
 - [Mental Retardation and Developmental Disabilities Branch, NICHD, Report to the NACHHD Council, June 2005](#)

Fogarty International Center (FIC)

- [Pathways to Global Health Research](#) (Draft)

Office of AIDS Research (OAR)

- [FY 2008 Trans-NIH Plan for HIV-Related Research](#)

Other Trans-NIH Plans

- [NIH Blueprint for Neuroscience Research](#)
(NCCAM, NCR, NEI, NIA, NIAAA, NIBIB, NICHD, NIDA, NIDCD, NIDCR, NIEHS, NIGMS, **NIMH, NINDS**, NINR, OBSSR)
- (NCCAM, NCR, NHGRI, NIA, NICHD, NIDA, NIDCD, NIEHS, NIMH, **NINDS**, NINR)
- [Research Plan for Tuberos Sclerosis](#)
(NCI, NHLBI, NIAMS, NICHD, NIDDK, NIMH, **NINDS, ORD**)
- [Muscular Dystrophy Research and Education Plan for the NIH](#)
(**NINDS, NIAMS, NICHD** [co-leads])
- [Action Plan for the Muscular Dystrophies](#)

- (**NINDS, NIAMS, NICHD** [co-leads])
- [*Report of the Brain Tumor Progress Review Group*](#)
(**NCI**, NINDS)
- [*Research Plan for Ataxia-Telangiectasia*](#)
(NCI, NCR, NEI, NHLBI, NHGRI, NIA, NIAID, NICHD, NIEHS, NIGMS, **NINDS**, ORD)
- [*The Autism Research Matrix*](#)
(**NIMH**; NICHD; NIDCD; NINDS; NIEHS; CDC; ACF; HRSA; CMMS; SAMHSA; NIDDK)
- [*NIH Research Plan on Down Syndrome*](#)
(**NICHD**, NCI, NHLBI, NIA, NIAID, NIDA, NIDCD, NIDCR, NIMH, NINDS)
- [*Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*](#)
(CC, CSR, NCCAM, NCI, NCMHD, NCR, NEI, NHGRI, NHLBI, NIA, NIAAA, NIAID, NIBIB, NICHD, NIDA, NIDCD, NIDCR, **NIDDK**, NIEHS, NIGMS, NIMH, NINDS, NINR, NLM)