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PROGRESS REPORT ON BRAIN RESEARCH

Introduction by Carlos Belmonte, M.D., Ph.D.

PERSPECTIVES ON SUBSTANCE ABUSE RESEARCH

Essay by Floyd E. Bloom, M.D.

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INTRODUCTION

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CARLOS BELMONTE, M.D., PH.D. / INTERNATIONAL BRAIN RESEARCH ORGANIZATION

Neuroscientists old enough to have a perspective on the progress in brain research over the last decades share with me the feeling that we are living a revolution. Revolutions profoundly change people's lives and often devour their own children, so that seminal discoveries made only a few years ago by prominent scientists are now anonymous and pushed aside by exciting new findings. But researchers must set aside nostalgia to address the now very real possibility of answering fundamental questions about the human brain—questions that seemed inaccessible not long ago.

We are still far from curing many of the major brain pathologies. Scientists and health administrators alike have repeatedly lamented the difficulties involved in translating basic research findings into human therapy, which are a source of frustration for basic and clinical neuroscientists. Yet an understanding of the molecular and cellular mechanisms underlying brain diseases is the most secure and rapid way of finding effective therapies for disease prevention and cure.

The Dana Alliance for Brain Initiatives' *Progress Report on Brain Research* acknowledges each year the exciting advances in neuroscience that are bridging the gap between basic research and clinical results. In the new format the report launches this year, a number of "hot spots" are selected for coverage, providing the reader with an up-to-date view of recent advances and their significance in the context of basic and clinical knowledge. The report's existence is the result of a strong belief in the importance of spreading scientific knowledge. More important, the report aims to broaden the audience for such research. The rapid progress in brain science provides continuous news about different aspects of brain function, which makes it difficult even for specialists to stay abreast of current findings. A publication that brings major advances in brain research to

neuroscientists, professionals, and lay readers alike in a readable and attractive form—while maintaining a high quality of scientific information—is an invaluable resource.

The Birth of Brain Awareness

In 1992, the Dana Foundation decided to share with the public the advances in brain research that were taking place in laboratories and hospitals around the world. After all, the public would be the ultimate beneficiaries of the progress made in knowledge of the brain.

The foundation promoted, first in the United States and later in Europe, the alliance of a group of distinguished neuroscientists who would commit themselves to public awareness of brain research and its potential and to the dissemination of information in a comprehensible and accessible way. Thus was born the Dana Alliance for Brain Initiatives. At that time, many active researchers in the neurosciences regarded the initiative with skepticism, thinking that the responsibility was too big for a private foundation and that it should rather be in the hands of public institutions and governments.

The popularity of Brain Awareness Week, and the success of the multiple publications and activities the world over, including the Dana Alliance's annual progress report, illustrates the error of that judgment. The foundation has succeeded in arousing in the general public the perception that neuroscience directly relates to their personal lives.

Treating the Disorders of Modern Life

This year, the report deals primarily with the advances achieved in the understanding of brain disturbances that have a particular incidence in modern societies, such as Alzheimer's disease, schizophrenia, and brain damage from blunt head injury. However, the report neglects neither the contribution of brain research to the understanding of other social problems, such as substance abuse and obesity, nor the discussion of opportunities offered by newly emergent technologies.

The recent hypothesis that Alzheimer's disease results from a dysfunction in neurons' ability to change their connections to one another represents an attractive augmentation to the dominant theories that focus on amyloid plaques and neurofibrillary tangles. Plaques and tangles may be consequences, rather than causes, of the disease.

So, too, have recent studies searching for the causes of schizophrenia pointed to new areas of brain activity—in this case, malfunctions related to the brain chemical glutamate—that may lie "upstream" of the causes proposed by older hypotheses.

In treating post-traumatic stress disorder, researchers have looked to new brain areas but also to new therapies and technologies aimed at attenuating persisting memories of traumatic events and reducing the direct effects of brain injury. These therapies range from memory recall through virtual reality to reduction of the cytotoxic effects of brain damage with drug treatments.

Like some symptoms of post-traumatic stress disorder, alcoholism, drug abuse, and excessive food intake were once thought to be the voluntary expression of character flaws, rather than pathologies of the brain. Today, scientists realize with increasing clarity the role of the brain's reward pathways in the compulsive intake of drugs and food. In cases of both obesity and alcoholism, scientists believe they have correctly identified the brain areas critical to behavioral control and susceptibility to abuse.

Control of a different sort has been key to advances in brain-machine interface, which aims to enable subjects immobilized by nervous system injuries to interact with the environment via external devices controlled by the electrical activity recorded from nerve or muscle cells. Thanks to progress made in recent years, this dream too is approaching reality.

Brain Science on a Global Scale

The variety and significance of the advances summarized in the 2009 *Progress Report* emphasize their potential for improving the lives of millions of persons afflicted by nervous system disturbances, and they serve to justify the efforts of scientists and funding agencies in brain research. However, the complementary role of neuroscience research in extending our knowledge about the mechanics of the normal human brain will in the long term have an equal or even larger influence on our lives. For example, concepts of legal responsibility and guilt, methods in education, or the possibility of external control of brain activity to modulate human behavior will be determined in the future by advances in brain research. The processes by which the brain generates consciousness and other complex cognitive functions are still unknown, but they are increasingly accessible to scientific

scrutiny and, judging from the rhythm of advances, are closer to being realized than we once thought. The social impact of a scientific understanding of human behavior will surely be immense, making the exploration of the brain the principal scientific challenge of the twenty-first century.

We must involve all countries of the world in the scientific adventure of exploring the brain. In a global community constantly brought to the brink of confrontation, science is a common territory where rationality is the principal moving force and where concepts and theories have to be experimentally confronted with reality to become accepted. Scientific research belongs among those few human activities guided by universally respected ethical values, and thus it offers a common ground on which to cooperate, individual differences and beliefs notwithstanding. Having this additional role for modern science in mind, brain research has emerged as a particularly exciting field to test the possibility of global cooperation.

PERSPECTIVES ON SUBSTANCE ABUSE RESEARCH

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No advances in brain research this year match the importance of those gains made in substance abuse research and treatment, detailed in the following chapter. Consider the recent development of several medications that can help drug-dependent individuals reduce their consumption of almost all of the legal and illegal drugs that humans administer to themselves. Such a feat merits special status even among the year's biggest scientific findings. But the subject also has several important lessons to teach us about the process by which researchers uncover the brain mechanisms affected by drugs, and about the role of experience in developing an addiction. In addition, scientists' improved understanding of the natural history of the disease of addiction—the average age of onset, the duration of dependence with or without treatment, and the influence of genetic and environmental factors in prolonging or shortening dependence—may help individuals decide when to seek treatment, and how.

Finding the Right Receptors

Recent surveys from the National Institutes of Health indicate that more than 22 million Americans have significant substance abuse problems, but fewer than 25 percent of these people receive treatment. More than 80 percent of federal and state prison inmates have been incarcerated for alcohol- or drug-related offenses. Those not treated while in prison are almost certain to return to addiction upon release.

Interest in drug addiction rose as a result of the intense use of heroin and marijuana by enlisted personnel in the Vietnam War, a trend that led President Nixon to create the Special Action Office on Drug Abuse Prevention in 1971. That step led the National Institute of Mental Health to increase research into both alcoholism and other forms of drug abuse. Epidemiological studies of the soldiers revealed that many of them were too young to purchase alcoholic beverages, whereas pure heroin and marijuana were cheap and readily available. At the time, scientists couched what little they knew about the intoxicating effects of beverage alcohol (ethanol) and the illicit addictive drugs such as heroin, cocaine, and marijuana in terms of indirect actions on the six neurotransmitters that were then under study (acetylcholine, dopamine, norepinephrine, serotonin, glutamate, and gamma-aminobutyric acid—GABA).

The newly stimulated research into addictive drugs first focused on the nature of the receptor at which opiate drugs initiated their effects in experimental animals. Once that receptor had been well characterized by several highly competitive groups of neuroscientists, some imaginative researchers began to consider why the brains of humans possessed such a drug receptor. In less than five years that train of thought yielded an astounding discovery: the opiate receptors existed because they represented the sites of action of previously unknown neurotransmitters, then termed "endorphins"—endogenous (naturally occurring) morphine-like substances. Eventually, scientists defined three separate endorphin gene families, expressed in three separate families of neuronal circuits together with three major kinds of endorphin receptors.

Attention Shifts to Alcoholism

These discoveries had two enormous effects on the neuroscience field. Some scientists took the discovery of an unknown transmitter whose receptors interacted with opiates as reason to suspect that other powerful central nervous system drugs, such as marijuana and benzodiazepines (drugs used to treat anxiety), produced their effects via receptors for other unknown transmitter systems in the brain. Not surprisingly, researchers soon identified endogenous cannabinoids, neurotransmitters whose cannabis receptors permit the actions of marijuana, while the effects of benzodiazepines were later attributed to a specific combination of the subunits that compose the receptors for GABA.

The second consequence of the discovery of the endorphin signaling systems concerned the scientific attention paid to alcoholism. Potent and selective antagonists that block opiate receptors had already been developed as a means to treat cases of opiate overdoses and addicts in federal prison hospitals. Experimentalists then began to look at other drugs whose basic workings were not yet understood, including alcohol.

Alcohol research in the 1970s suffered from a lack of interest from researchers. Compared to the potency of other sedative drugs, alcohol was considered quite weak in terms of potency, as grams of alcohol were required for the anxiety-reducing effects and tens of grams for the intoxicating effects. Yet, by the early 1980s, several groups of researchers had reported that opiate antagonists would suppress alcohol self-administration in animal models and would reverse the effects of low doses of ethanol on neurons in brain tissue samples.

These studies on alcohol then converged with scores of related studies that highlighted specific regions of the brain as a drug reward circuit—the dopamine neurons of the substantia nigra and a small cluster of neurons in the anterior hypothalamus known as the nucleus accumbens. These studies, well covered in the chapter that follows, replicated highly consistent findings that opiate antagonists could reduce alcohol self-administration in animal models. The results emboldened clinicians to try the drugs on alcohol-dependent human subjects, who evidenced an almost complete lack of side effects. Eventually, the FDA approved the use of opiate antagonists and other drugs that reduce the pharmacological effects of alcohol on cells for the clinical treatment of alcohol dependence.

Fighting Addiction Misinformation

To return to the enlisted men of the Vietnam War: In the 1970s, and indeed even now for many who consider themselves informed, drug addiction was considered by law enforcement officers and the criminal justice system to be instant and permanent, inducing a craving so powerful that no conscious effort could overcome it. To those addicts in withdrawal, overtly criminal behavior to acquire drugs was considered justifiable. However, when large samples of soldiers were reinterviewed one and three years after their service and compared with an age-matched group, the results were astounding. While initial interviews supported by urine testing indicated that nearly 80 percent

had used marijuana, that half of all enlisted men had tried morphine or opium, and that nearly 20 percent were symptomatic enough to have been called dependent while in service, one year later only 5 percent of those who were addicted to opiates in the war zone were addicted in the United States. Of those not addicted, virtually none had received any treatment. Lee Robbins of Washington University in St. Louis, the lead epidemiologist of those studies, concluded that the availability of cheap drugs accounted for the high rates of drug use in wartime. Clearly, the common view of the addict—once addicted, addicted for life—was erroneous. Addiction was not a lifelong dependency; it could be interrupted by a change in environment. Perhaps with the right agent treatment was possible. For the veterans who exhibited deviant social behavior before serving in Vietnam, however, the rates of re-addiction and treatment failure were as high as in the civilian and federal prison populations.

In the case of alcohol dependence, the lifetime prevalence approaches 20 percent in the general population. (The genetic basis for vulnerabilities and resistance to addiction are another important, active area of work, but that is beyond the scope of this essay.) With regard to licit drugs, among the causes of deaths in the United States as listed in the Physicians and Lawyers for National Drug Abuse Policy 2008 report, smoking-related deaths are number one, and alcohol-related deaths are number three, after cancer.

The Road to Better Treatment

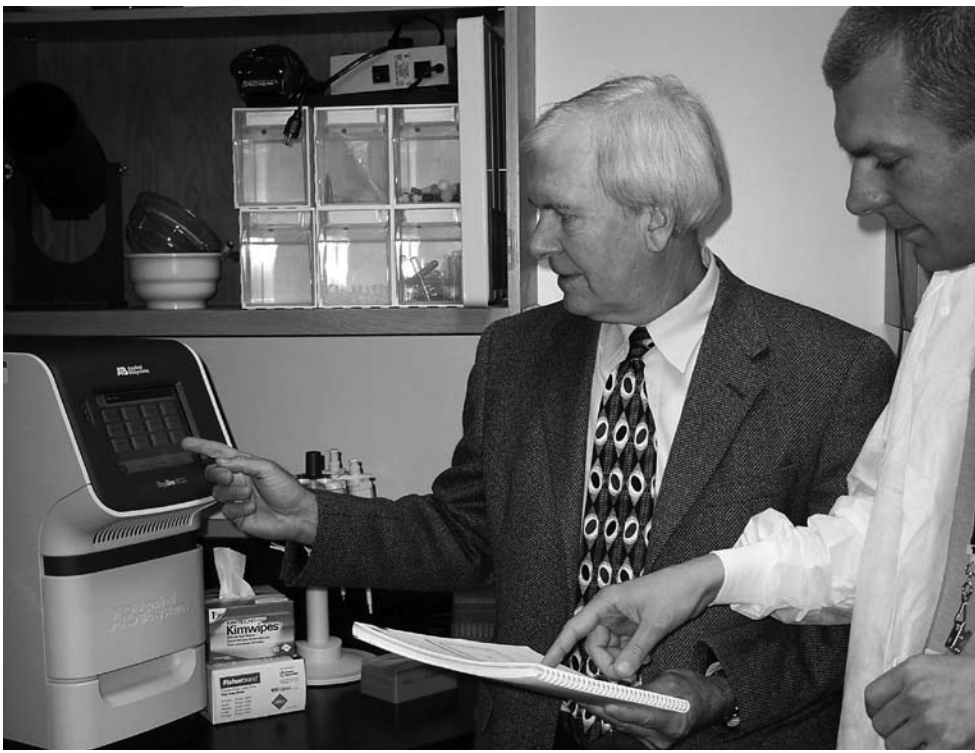
The development of drugs to treat alcohol-dependent subjects has opened the door to the search for medications to treat other dependencies. However, most physicians have never received training in the diagnosis or treatment of dependent patients. Subjects arrested for driving while intoxicated and brought to emergency rooms are placed in a double bind, since most health insurance policies by law in many states will not cover treatment of intoxicated subjects. Most physicians—if they have the time to speak with their patients, diagnose the dependency, and then decide to embark on a therapeutic course—may not believe that medication is either helpful or required, holding the view that counseling alone, by some third-party practitioner, will suffice. While opiate antagonists combined with group therapy in clinical trials have been reported to be quite effective for dependent populations who seek treatment, far more addicted individuals have

not yet opted for treatment. Gaining access to a health care system unaware of the treatments that could be implemented is not much help. However, sufficient attention from the patients who recognize the problem in themselves or a significant other may ultimately bring these advances of medical treatment more effectively to the population at risk. Clearly this field has progressed significantly in recent years, thanks in no small part to biomedical research.

PROGRESS IN BRAIN RESEARCH IN 2008

SUBSTANCE ABUSE
Mapping the Pathway of Addiction

Elizabeth Norton Lasley



Raymond F. Anton (left) and Gabor Oroszi in the lab at the Medical University of South Carolina
(Raymond F. Anton, M.D. / Medical University of South Carolina)

For several decades, research has been suggesting that substance abuse is a disorder with neurobiological underpinnings. Several medications are already available to treat alcoholism, and more are in the pipeline. Findings in 2008 show that different types of addiction may have genetic roots. One line of research shows that an alcoholic patient's response to treatment may hinge on variations in a key receptor. Another effort reveals distinct pathways of alcoholism, brought about by separate neural circuits. In the future, treatments will be targeted to the type of addiction a patient has, pinpointing the approach that will be most successful for each individual.

Although progress in 2008 centers on the roots of alcoholism, the implications could shed new light on understanding addictions in general. In fact, studies of alcoholism and other types of addiction are occasionally, sometimes surprisingly, intertwined.

Homing In on the Opioid Receptor

Much of the scientific knowledge of substance abuse centers on the opiate drugs. These include opium itself—an extract of the poppy plant known since ancient times for its superior pain-relieving qualities—and its derivatives, including heroin, morphine, and codeine. The opiates have a downside, however: the potential to cause addiction. In the first half of the twentieth century, researchers directed their efforts toward finding a drug that rivaled the painkilling power of the opiates but did not carry the addictive potential. To date, they have found none.

Despite these efforts, interest in treating addictions lagged during that half-century. According to Ting Kai Li, director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), not only addiction but behavioral research in general was slow to be regarded as a subfield of neuroscience. Behavior was widely considered voluntary—a choice, for good or bad—and not the result of brain processes.

"It's true that drinking or drug use may start out as voluntary behavior," Li observed, "but for some people what's voluntary may become habitual and, finally, compulsive."

The question of what happens in the brain to cause addiction became a priority when the government declared a "war on drugs" in the 1970s. To find answers, the NIAAA and the National Institute on Drug Abuse (NIDA) were founded in the early 1970s.

One of the first milestones in addiction research resulted from

this initiative. Scientists had already developed several successful opiate antagonists—structurally similar compounds that (presumably) latched onto the same receptor as opium, either blocking or reversing its actions. These included naloxone, a rapid-acting compound used to treat overdoses, and a longer-acting version called naltrexone. But the future of addiction research was limited by the fact that the receptor itself was still undiscovered. "They were working in the dark," said Charles O'Brien, director of the University of Pennsylvania's Center for Studies in Addiction. The first opiate receptor was officially identified in a 1973 NIDA-sponsored study by Solomon Snyder and Candace Pert at Johns Hopkins University.[1]

Chemical Messengers in Addiction

Scientists had found no apparent reason for the human brain to contain receptors for a plant extract. The brain did have its own repertoire of chemicals—about a dozen had been identified by the mid-1970s. But many researchers suspected that the opioid receptor interacted with an unknown brain chemical, which opium resembled sufficiently to bind to the same receptor.

This view was confirmed in 1975, when two researchers from Scotland, John Hughes and Hans Kosterlitz of Scotland confirmed this view in 1975, isolating the chemical structure of an endogenous, opiatelike neurotransmitter they called enkephalin.[2] The word "endorphin" (short for "endogenous morphine") was already in general use and became the better-known term for the brain's naturally occurring painkillers. These findings raised hopes—both in the scientific community and among legislators—that addiction could be treated medically. Studies over the next three decades culminated in a 2008 finding showing that an alcoholic patient's response to the opiate antagonist, naltrexone, may be linked to the patient's genetic makeup.

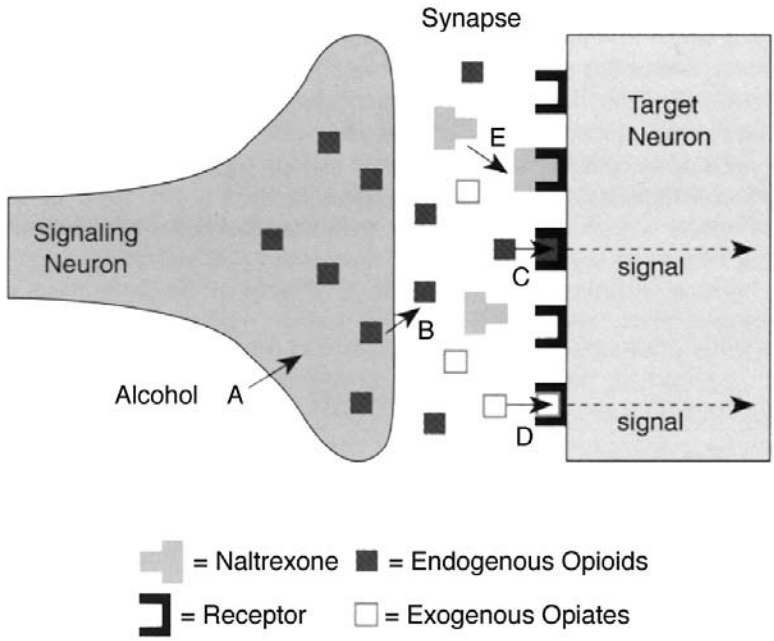
A Surprise Connection

A bit of context will illustrate the significance of this finding. In 1980, the scientific community was jolted by a study of rhesus monkeys showing that naltrexone helped quash the desire for alcohol. At the time, little was known about alcohol's effects on the brain; the prevailing dogma held that opioid receptors were not involved. "As is always

the case with basic research, something turned up that no one would have dreamed of," said O'Brien. Other studies upheld the finding, however—including many studies of naltrexone in human alcoholics conducted by O'Brien and colleagues—and in 1995 naltrexone won FDA approval as a treatment for alcoholism.

In 2003, O'Brien led a study that linked naltrexone response with a specific genetic variant of the mu-opioid receptor.[3] This receptor type is widespread throughout the body, including the reward areas of the brain, and is thought to play a role in the adaptive changes that accompany chronic drug or alcohol use. Specifically, O'Brien's team examined the DNA from participants in several published studies. Individuals with the genetic variant were less likely to relapse into drug use after treatment.

O'Brien's findings were confirmed in 2008, in a multicenter study of more than 900 patients, reported by Raymond Anton of the University of South Carolina and colleagues.[4] The paper appeared in



A) Alcohol is thought to stimulate the release of endogenous opioids, which may produce the euphoric feelings associated with alcohol consumption. B) Endogenous opioids are released into the synapse and C) stimulate activity at opiate receptors, which produces a signal in the target neuron. D) Exogenous opiates such as morphine also stimulate opiate receptors. E) Naltrexone is thought to block opioids from activating opiate receptors. (Joseph Volpicelli / NIH National Institute on Alcohol Abuse and Alcoholism)

the February issue of *Archives of General Psychiatry* (a journal that rejected the original 1980 naltrexone study, as O'Brien noted in an accompanying commentary).

Just how alcohol works at the opioid receptor remains a mystery, but it seems to produce its high by stimulating endorphins, which, in turn, drive up dopamine levels in the brain's reward pathway—a relay that's effectively blocked by naltrexone. When experimental animals accustomed to alcohol are first given naltrexone, the endorphin-induced buildup of dopamine in the reward pathway is curtailed. Human subjects, too, report less of an alcoholic buzz when given naltrexone.

"Naltrexone responders" seem to share certain traits. Their cravings for alcohol are especially intense, and they have a strong family history of alcoholism. They begin drinking young and can outdrink everyone else. On a biochemical level, their endorphin response is more marked than that of nonresponders.

In the 2008 study, alcoholic patients with the genetic variant who received naltrexone were able to go for more days without a drink, had fewer days where they drank heavily, and were better able to abstain from alcohol or drink only moderately for the last eight weeks of the sixteen-week study. On the other hand, among patients without the variant, those given naltrexone showed no more improvement than did the placebo-treated group.

"These findings put us on the verge of an important therapeutic development," said O'Brien. "Right now an alcoholic is someone who drinks too much. But we may soon be able to identify subsets of patients who respond very differently to treatment depending on the mechanisms of their addiction."

Li of the NIAAA agreed. He points out that currently, according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*), the standard handbook for mental health professionals, an alcoholic is someone who meets three of seven criteria, a list that includes loss of control when drinking, tolerance, and withdrawal syndrome. "If you have only two of the seven factors you're not an alcoholic. If you have three—any three—you are," Li said. In the future, alcoholism may be classified and quantified, using both the patient's genetic profile and personal characteristics to come up with the best possible treatment.

Only two other drugs have been approved to treat alcoholism. Acamprosate has shown modest success in easing withdrawal symptoms; though it is widely used in Europe, U.S. studies have questioned

its efficacy. The earliest treatment, disulfuram (Antabuse), blocks the metabolism of alcohol, leading to the buildup of a toxic compound. The results are unpleasant: flushing, palpitations, nausea, and vomiting. Li, who has worked with alcoholic patients using disulfuram, found the approach effective if the drinker was strongly motivated, or compelled by law (after a drunk driving conviction, for example) to take it. But the unpleasant effects are easily avoided by simply not taking the drug. Disulfuram remains a deterrent, not a cure.

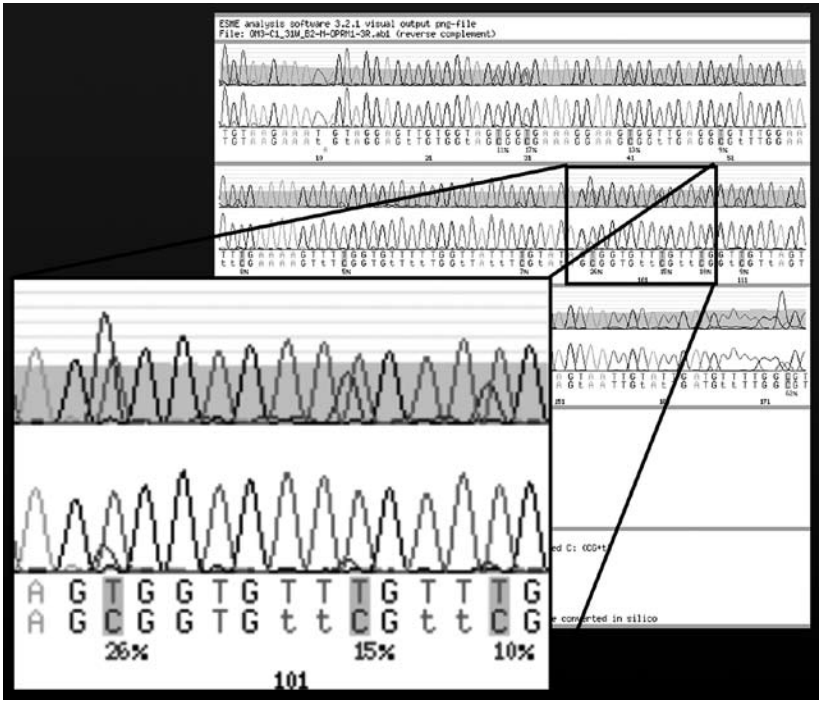
Genetic Profiles of Addiction

Other 2008 findings support the possibility that future treatments could be genomically based. In the April 23 *BMC Medical Genetics*, as part of a larger study of substance abuse among American Indians, Cindy Ehlers and colleagues at The Scripps Research Institute reported a connection between mu-opioid receptor variants and the effects of alcohol.[5]

Participants from eight reservations gave blood samples and completed diagnostic interviews describing their response to alcohol. Subjects who had more-intense or unpleasant feelings after two or three drinks—such as clumsiness, dizziness, nausea, or discomfort—were likely to have at least one of seven individual variants of the mu-opioid receptor. Because they reported more-unpleasant experiences with alcohol than did those without the variants, these participants were less likely to drink, suggesting that the genetic configuration of the receptor conferred resistance to alcohol.

A study of former heroin addicts showed an "epigenetic" alteration of the mu-opioid receptor, possibly increasing susceptibility to addiction. This type of alteration, which affects the gene's function but not the DNA sequence (and so is not a "mutation" in the strict sense of the term), may be either genetically inherited or drug-induced. Studies of humans and animals show that substances of abuse, including alcohol, nicotine, and cocaine, can affect a biochemical alteration process called DNA methylation. In the July 23 *Neuropsychopharmacology*, David Nielsen and colleagues at Rockefeller University looked at a specific site in the promoter region, which controls gene expression, and found significantly higher alteration of the mu-opioid receptor gene in former heroin addicts as compared with controls.[6]

Two drugs already in use may reduce methylation—azacitidine, used to treat a group of blood diseases, and valproic acid, an anticonvulsant



The computer-analyzed output from a gene sequencing procedure shows changes in the genetic structure of the mu-opioid receptor gene in former heroin addicts undergoing methadone treatment. (David Nielsen, Ph.D. / Rockefeller University)

used to treat epilepsy and bipolar disorder—and may be a therapeutic option for addiction. Because DNA methylation may be influenced through many routes, including inheritance, environmental events, and drug exposure, the potential benefits of such an approach extend beyond just patients with a specific genetic configuration.

The Other Side of Alcoholism

Research in 2008 sheds light on another broad category of patients—the ones who do not respond to naltrexone. These patients, who may represent the majority of alcoholics, don't get more of an alcoholic buzz than most people; in fact, getting drunk is not their goal. Typically they indulge only moderately until later in life, when they escalate their drinking in response to stress, anxiety, grief, or health problems. For these users, heightened dopamine effects in the reward pathway are not the explanation. Instead, alcohol begins as a coping tool but soon disrupts the very circuitry with which the brain responds to stress. In what neuroscientist George Koob of The

Scripps Research Institute describes as the "dark side" of substance abuse, these drinkers suffer more intensely from the discomfort of withdrawal. Quitting becomes a stressor in itself, which only the forbidden substance can relieve.

This line of research shares its beginnings with the 1975 discovery of endorphins. Endorphins belong to a class of chemical messengers called neuropeptides—short chains of amino acids, the building blocks of proteins. Many researchers suspected not only that the brain produced neuropeptides but that some of them acted as hormones—secreted by a part of the brain called the hypothalamus into the bloodstream, then acting on the pituitary gland to touch off a variety of hormonal responses.

One such neuropeptide, corticotropin releasing hormone (CRH), was discovered in 1983 by Wylie Vale of the Salk Institute.[7] When secreted from the hypothalamus into the bloodstream, CRH acts on the pituitary gland to mobilize components of the body's stress response, such as the endocrine and immune systems. This discovery helped reveal many of the biological underpinnings of stress and stress-related illness. But CRF also acts within the brain itself, in areas that play a role in both stress and addiction.

Koob and others have shown that the brains of rodents accustomed to alcohol have overly active stress pathways. In particular, the effects of CRH are exaggerated in a region called the amygdala, a nexus of both fear and memory. A 2008 study published in *Biological Psychiatry* by Markus Heilig, a former student of Koob's who is now at the NIAAA, found evidence of a link between stress, alcohol, and CRH activity.[8] The investigators found that in rats that are accustomed

Markus Heilig and colleagues found that mice accustomed to alcohol are more likely to drink it when their stress pathways are stimulated. (Markus Heilig, M.D., Ph.D. / National Institute on Alcohol Abuse and Alcoholism)

to alcohol but are currently "on the wagon," a subsequent stressor makes the rats more likely to drink alcohol when it becomes available; the animals also have heightened fear responses and increased levels of CRH receptors in the amygdala.

The same may be true of humans, according to another 2008 paper, again in *Biological Psychiatry*. A team of researchers in Germany and England found that adolescents with certain variants of a CRH receptor resorted to heavy drinking after a stressful life event, such as difficulty with family, school, living conditions, or legal troubles.[9] The study is the first in humans to link a CRH gene with stress and alcohol abuse.

"The CRH work provides compelling evidence that a genetic variant can predict who is likely to be the second type of alcoholic—the ones who don't drink to feel good but because they feel even worse when they stop," said Koob. Unlike the naltrexone responders, however, these alcoholics do not have a treatment currently available. Experimental chemicals that block CRH receptors are not feasible options for humans.

A related pathway, however, holds promise as a possible therapeutic target. The stress-induced increase of CRH activity in the brains of alcoholics has been shown to trigger changes in another neurotransmitter, called substance P. The receptor for this chemical messenger, called the neurokinin (NK-1) receptor, has a known antagonist already in use in clinical trials. In the March 14 *Science*, another team led by Heilig showed that in recently detoxified "anxious alcoholics" a drug that attached to the NK-1 receptor (thus blocking the effects of substance P) blunted the patients' cravings for alcohol, including those brought on by stress.[10] Imaging studies showed that the effects of alcohol in key emotional centers of the brain were reduced among the study subjects compared with untreated alcoholics. NK-1 antagonists have been safely used in an effort, albeit unsuccessful, to relieve symptoms of depression and may become an important treatment for stress-induced alcoholism.

Addiction, Then and Now

The first written records of the pleasures of alcohol date to 4,000 B.C., when recipes for fermented beverages appear in writings from China, Egypt, and Sumeria. Ancient Greek and Roman gods were sometimes depicted carrying poppy plants, the original source of opium. Modern,

synthetic forms of opiates used for the relief of severe pain seldom result in compulsive drug-seeking behavior. But recreational use of opiates has long been known to be both destructive and addictive. In 1821, Thomas De Quincey published an essay called "Confessions of an English Opium Eater," in which the drug's pain-relieving effects paled in comparison to the euphoria it produced. De Quincey's essay sparked a fad of opium use by celebrities of the day, including the poets Elizabeth Barrett Browning and Samuel Taylor Coleridge (the poem "Kubla Khan" was written under the drug's influence); both quickly became addicts. Injected morphine, a highly purified opium extract, was first widely used for pain relief during the Civil War; so many soldiers came home addicted that morphine addiction became known as "the soldier's disease."

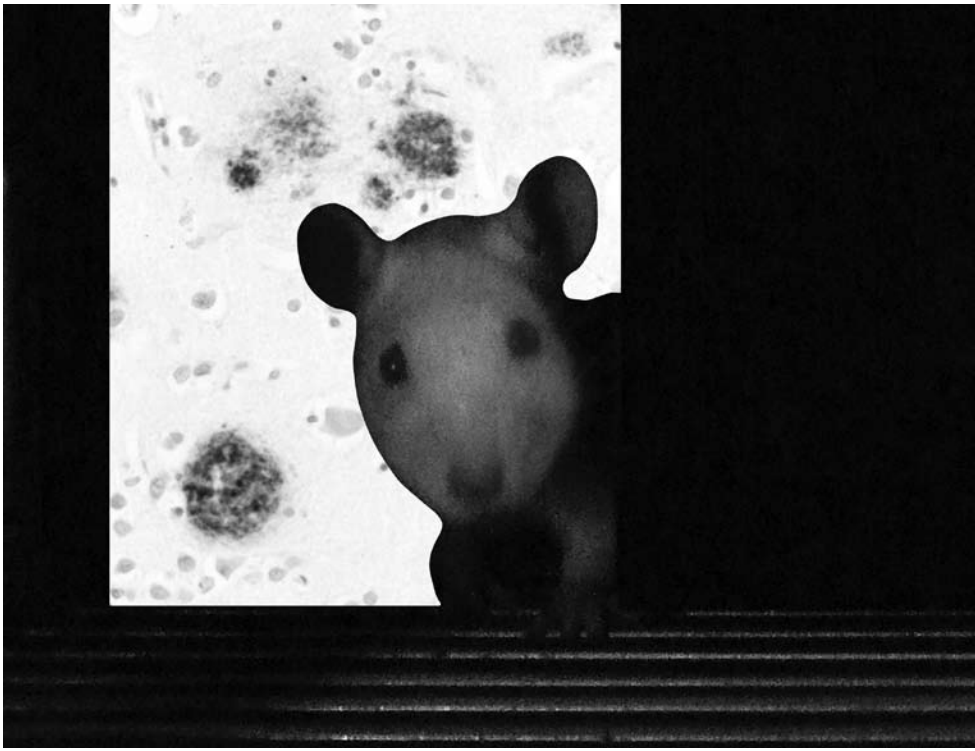
By illuminating the pathways of addiction in the brain, research continues to dispel the long-perceived link between substance abuse and pleasure-seeking (even in Roman times, the poet Seneca defined drunkenness as "nothing but voluntary madness"). Experts agree that recent findings in addiction research signal a change of fortune in what has traditionally been a challenging field in which to make progress, and may have profound implications for the future. For example, the naltrexone research may extend beyond alcoholism. "The fact that an opioid receptor can predict which alcoholic patients will respond to treatment with an opiate receptor antagonist suggests a shared fundamental mechanism in substance abuse," said Li.

Koob added that recent advances extend beyond addiction research. "Whatever we discover about how emotional systems are disrupted by addiction will carry over into other areas of research, including anxiety, depression, post-traumatic stress disorder, and possibly schizophrenia."

NEW DIRECTIONS FOR ALZHEIMER'S DISEASE RESEARCH

Successes and Setbacks

Tom Valeo



A rat whose memory has been impaired by a cerebral injection of beta-amyloid protein from the plaque-rich brain (background) of an Alzheimer's patient
(Ciaran Regan, Ph.D., D.Sc. / University College Dublin; Cynthia Lemere, Ph.D. / Harvard Medical School)

Clinical studies completed in 2008 caused scientists to raise provocative questions about the "amyloid cascade hypothesis," which has guided a generation of researchers in their quest to cure Alzheimer's. Though most current research still follows the path charted by this theory, efforts toward an effective treatment will require new navigation.

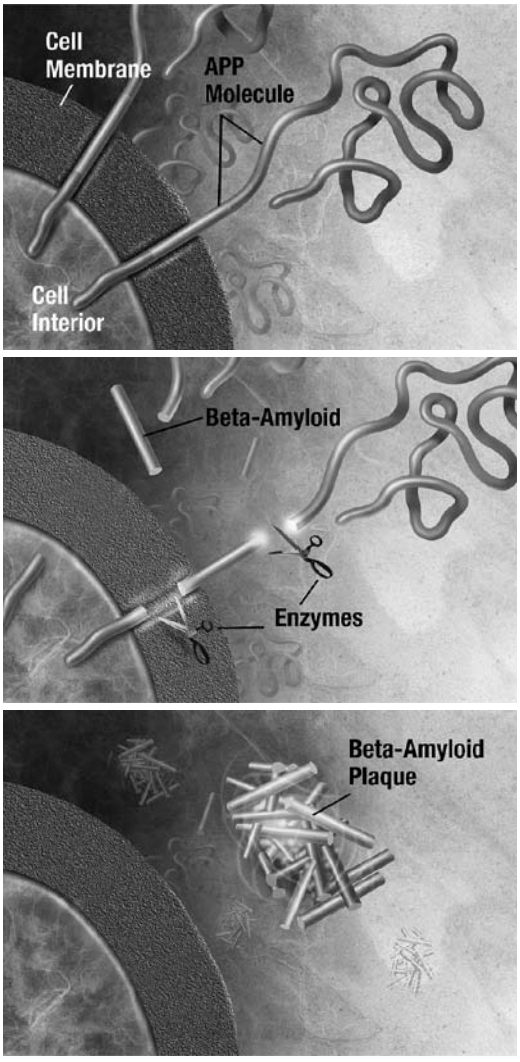
The Early Days of a Hypothesis

The amyloid hypothesis began to take shape in 1986 when scientists discovered a gene on chromosome 21 that produces amyloid precursor protein (APP), a substance of uncertain function found mostly in the space around neurons and produced abundantly in the healthy brain.[1] The APP gene contains the sequence for the peptide amyloid, which is concentrated in the plaques used to diagnose Alzheimer's brain pathology. People who inherit a form of early-onset Alzheimer's have a mutation on chromosome 21 in the APP gene that results in overproduction of the amyloid peptide. People with Down syndrome, who invariably develop Alzheimer's in middle age, have an extra copy of chromosome 21 containing the gene for APP, causing them to produce excess amounts of the protein as well.[2]

A variety of enzymes in the brain normally clip APP into harmless fragments that float freely between neurons, possibly contributing to the ability of neurons to form new connections with each other—a brain function that is vital to memory. However, specific "beta" and "gamma" enzymes—the presence of which is predicted by the mutations in the APP gene—clip APP so as to yield amyloid peptide. For reasons unknown, amyloid aggregates to form toxic strings known as oligomers, and it is hypothesized that these disrupt the transmission of signals at the synapse—the gap where signals jump from one neuron to another with the help of chemical neurotransmitters.[3]

According to the amyloid hypothesis, the toxic oligomers eventually accumulate into immobile clumps of protein known as beta-amyloid, or "senile plaques." Alois Alzheimer found these in the brain of a profoundly demented woman who died in 1906.

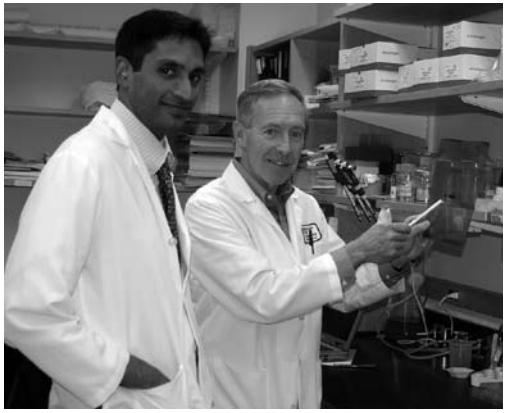
One hypothesis suggests that plaques act like magnets that attract and immobilize toxic oligomers, preventing them at least temporarily from committing mischief. However, the plaques themselves trigger damaging inflammation that contributes to the dysfunction and death of nearby neurons.



A genetic mutation predicts the presence of certain enzymes—shown here as scissors—that clip strands of APP into fragments that clump together in beta-amyloid plaques.
(NIH National Institute on Aging)

Researchers have devised a variety of ways to clear toxic oligomers from mice, but in human tests such treatments have failed to slow the memory loss, confusion, and other cognitive problems that afflict people with the disease. Though researchers and patients hope for new treatments from this line of study, they may be wrong to assume that significantly slowing down Alzheimer's progression is even possible in patients who already display the symptoms necessary to qualify as a trial patient.

"FDA guidelines generally suggest that one conduct trials first in mild-to-moderate Alzheimer's patients," said Dennis Selkoe of Harvard University, a pioneer in the development of antibodies



Ganesh Shankar (left) and Dennis Selkoe found that injecting toxic oligomers into rodents impaired the animals' memory.
(Dennis Selkoe, Ph.D. / Harvard University)

against toxic oligomers. "But by that time plaques, tangles, gliosis, and neuritic dystrophy are relatively advanced." (Gliosis is the accumulation of glial cells, which clear debris left by neurons when they die. Neuritic dystrophy refers to deformed neurons.)

The free-floating toxic oligomers appear to disrupt synaptic function years if not decades before symptoms of Alzheimer's appear. Selkoe reported in a 2008 paper that toxic oligomers taken from the brains of Alzheimer's patients and injected into rodents profoundly disrupted synapses and impaired memory.[4] More distressing, toxic oligomers, though they are certainly part of the problem, may not be the right target for treatment at all—plaques may be forming in response to something else entirely.

Conflicting theories and disappointing results prompted two veteran Alzheimer's researchers, Peter H. St. George-Hyslop of the University of Toronto and John C. Morris of the Washington University School of Medicine in St. Louis, to ask recently in the journal *Lancet* if the past two decades of anti-amyloid research "were spent barking up the wrong tree."[5]

Such pessimism is premature, other scientists argue. Some, such as Selkoe, believe that anti-amyloid therapies would be far more effective if started earlier, before the toxic oligomers have had time to damage synapses and kill neurons. Others have been intensifying the search for subtle indicators in blood or cerebrospinal fluid, or perhaps on magnetic resonance imaging scans, that would indicate the earliest signs of pathology and perhaps allow for the prevention of the accumulation of toxic oligomers.

Anti-amyloid Drug Disappoints

Without such biomarkers, treatment will be limited to people with overt symptoms of Alzheimer's, and judging from clinical trial results reported in 2008, such people do not respond very well to efforts to remove toxic beta-amyloid from their brain. Myriad Genetics, for example, tested an anti-amyloid drug called tarenflurbil (Flurizan) in patients with Alzheimer's. After investing $200 million to develop the drug, the company announced in 2008 that it was suspending all further research because an eighteen-month study involving 1,684 patients—the largest Alzheimer's treatment trial ever—showed that it did not produce significant improvement in memory, cognitive functioning, or the ability to perform activities of daily living such as dressing and bathing.[6] The trial did not include tests to detect how much beta-amyloid, if any, was removed from participants.

Elsewhere, follow-up studies have been conducted in patients who participated in clinical trials to test the effectiveness of AN-1792, a vaccine against Alzheimer's developed nearly a decade ago by Elan Pharmaceuticals in cooperation with Wyeth Pharmaceuticals. After conducting one follow-up, Clive Holmes, of the Memory Assessment and Research Centre in England, concluded that "progressive neurodegeneration can occur in Alzheimer's disease despite removal of plaque."[7] But the data from a larger follow-up study included tantalizing hints of benefit in those patients who responded to the vaccine by producing antibodies against beta-amyloid. "Patients who still had antibodies in their system at the time of the follow-up did significantly better on activities of daily living, and on a measure of dependency," said Dale Schenk, executive vice president and chief scientific officer for Elan.

Work on AN-1792 was abandoned because it produced serious cerebral inflammation, but Elan and Wyeth have since developed an antibody that attacks beta-amyloid. The eagerly awaited results of a clinical trial of the drug, which bears the unwieldy name of bapineuzumab, were announced at the International Conference on Alzheimer's Disease meeting in July. The antibody reduced brain atrophy and produced some improvement in mental functioning, primarily among patients who did not possess the gene for ApoE4, the strongest genetic risk factor for Alzheimer's disease. (About 25 percent of humans carry one or two copies of the gene for ApoE4, but more than half of those with Alzheimer's carry the gene.) Researchers

did not expect the Phase II trial, designed to test for and define safe dose ranges for the antibody, to reveal efficacy in any subgroups. In this respect the study was a success.

However, those in the study who possessed the gene for ApoE4 were barely helped at all. "Perhaps there's a biological difference between carriers and noncarriers (of the gene)," said Sid Gilman, the neurologist who served as the chair of the independent safety monitoring committee for bapineuzumab, as he announced the findings. "Or perhaps carriers have a greater density of beta-amyloid."

Or maybe, according to a growing number of researchers, the amyloid hypothesis needs further refinement. "There are several chinks in the armor of the amyloid hypothesis," said David Morgan, director of the Alzheimer's Research Laboratory at the University of South Florida. "But the question isn't whether the amyloid hypothesis is correct. Every gene mutation we know of that causes Alzheimer's in a dominant fashion modifies the production of amyloid, and there are 100 genes that do this. That seems to provide pretty compelling evidence that amyloid plays a role. The question is whether targeting amyloid will be efficacious."

What Is 'Normal Aging'?

The original amyloid hypothesis, which emphasized the presence of amyloid plaques, contained one glaring inconsistency: the number of plaques found in elderly brains does not correlate very well with cognitive difficulties. A much stronger indicator is the other hallmark of Alzheimer's, the tangles of tau protein found within neurons.

This has led to debate between "tauists," who believe that tau protein causes Alzheimer's, and "BAPtists," who blame the beta-amyloid protein found in brain plaques. The tauists have always had a compelling case. Tau is a crucial brain protein found in the microtubules that act like railroad tracks for transporting neurotransmitters from the cell body to the synapse, where the neurotransmitters are released. Any dysfunction involving tau is catastrophic for the brain, as several "tauopathies," including Alzheimer's, vividly demonstrate.

Today, researchers generally agree that toxic beta-amyloid initiates the dysfunction that leads to tau degeneration, but the most potent trigger by far is age. The aging process plays such a large role in Alzheimer's that Peter Whitehouse, the geriatric neurologist who founded Case Western Reserve University's Memory and Aging

Center, published a book in 2008 titled *The Myth of Alzheimer's*, in which he argues that the disease is nothing but normal brain aging that takes place faster in some people than in others.[8] Everyone, he believes, would get Alzheimer's if they lived long enough.

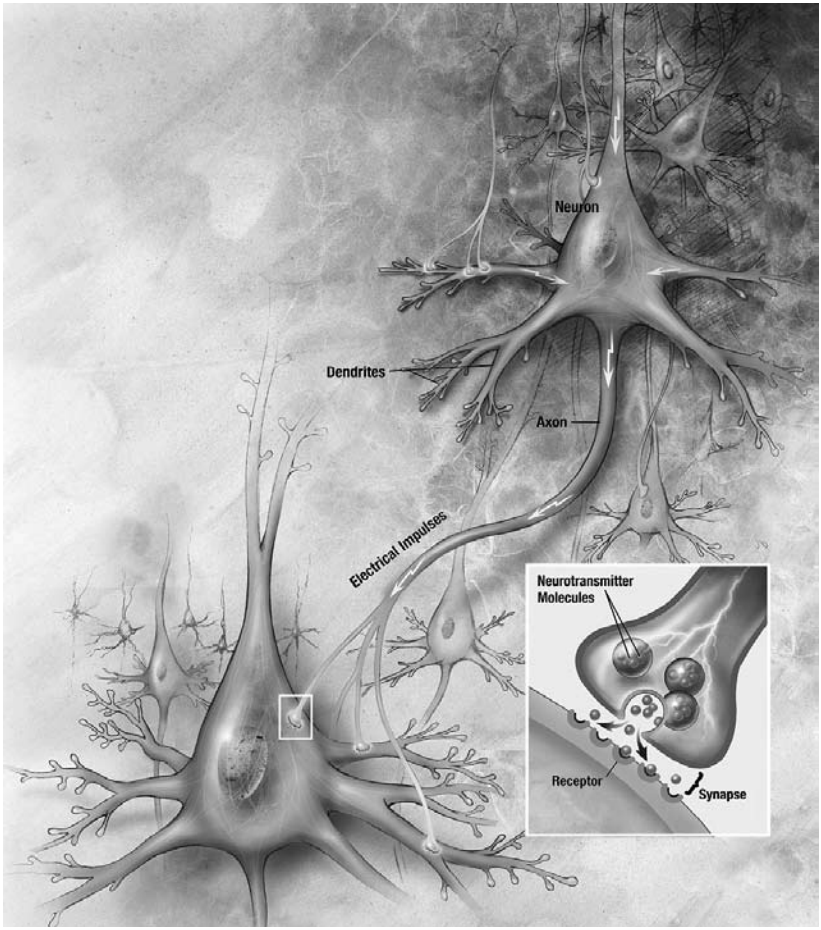
But strong evidence contradicts this assertion. For example, Juan Troncoso, codirector of the Alzheimer's Disease Research Center at Johns Hopkins University, has demonstrated that one region of the hippocampus known as CA1, which is crucial for the formation of short-term memories, remains stable in old age among those who do not have Alzheimer's, but degenerates drastically in people with Alzheimer's.[9]

In addition, some people live to extreme old age with only minor loss of mental acuity. An article published in 2008 about the autopsy performed on the world's oldest woman, who died at the age of 115, reported that her brain was virtually free of signs of Alzheimer's.[10] Clearly Alzheimer's is a disease, not normal aging. Yet the incidence of Alzheimer's disease increases in lockstep with aging, producing at least subtle symptoms in about half of all people by the age of 85. Somehow, the aging process must contribute to Alzheimer's.

Combining New and Old Theories

One idea gaining ground involves synaptic exhaustion. Neurons communicate with each other by releasing neurotransmitters from the synapse. Receiving fibers known as dendrites, which branch like tree boughs from nearby cells, are stimulated by neurotransmitters and propagate the impulse, which travels to the cell body and then down that cell's axon. Neurons create new synaptic connections among themselves constantly, and this process is energy-intensive.

Few regions of the brain work harder at this than the hippocampus, where short-term memories form—and where Alzheimer's begins. In 2008, Randy Buckner of Harvard and two colleagues published a paper in which they observed an uncanny similarity between hippocampal changes and those in another area affected by early Alzheimer's: the brain's "default network"—regions at the front and rear of the brain connected by long fibers.[11] The default network becomes active when the mind wanders and slips into what William James, the founder of modern psychology, dubbed the "stream of consciousness." Since the mind wanders whenever it is not busy, the default network is one of the busiest areas of the brain. In people with Alzheimer's, glucose



Neurons communicate by transmitting chemicals at the synapse, a process that becomes sluggish in brains with Alzheimer's because of a drop in glucose metabolism. (NIH National Institute on Aging)

metabolism in the default network drops significantly, suggesting that synaptic transmissions are becoming sluggish. This drop in the brain's use of glucose continues as the disease progresses, and it correlates with the severity of dementia. In addition, people who possess the gene for ApoE4 show lower glucose metabolism in these areas much earlier in life, suggesting that dysfunction begins years or perhaps decades before the first symptoms appear.

This "metabolism hypothesis," as Buckner calls it, corresponds with a conception of Alzheimer's disease long promoted by Marcel Mesulam, director of the Cognitive Neurology and Alzheimer's Disease Center at Northwestern University Medical School in Chicago. Mesulam, who presented a spirited explanation of his idea at

the International Conference on Alzheimer's Disease meeting in July, believes that Alzheimer's evolves from the breakdown of neuroplasticity, the process by which synapses form new connections with other neurons. The rapid breakdown and buildup of connections demands a vigorous repair process, and that, Mesulam believes, is what slows down and eventually produces the "cascade" of degeneration that leads to Alzheimer's disease. Every cause of Alzheimer's disease ever proposed—including head trauma, the ApoE4 gene, cardiovascular disease, inflammation, stroke, and aging itself—interferes in some way with neuroplasticity, he said. Mesulam first proposed his hypothesis nearly a decade ago in an effort to solve what he calls the "central puzzle" of Alzheimer's—the genetics of the disease point to beta-amyloid as the cause, but the symptoms coincide more closely with the number of tau protein tangles found within neurons.

A revised version of the amyloid cascade hypothesis links these two phenomena by accusing toxic beta-amyloid oligomers of disrupting activity at the synapse, creating stress that leads to the breakdown of the tau protein "tracks" that guide neurotransmitters. In 2006, two researchers at the University of Virginia, Michelle E. King and George S. Bloom, found that beta-amyloid triggers the disassembly of tau microtubules.[12] They are preparing to publish more-detailed research on the biochemistry behind this synaptic dysfunction. "We think the breakdown of microtubules in axons caused by the interaction between amyloid and tau simply slows down or halts the replenishment of the proteins involved in making neurotransmitters," Bloom said. "If these proteins are not replaced, the synapse can't function properly. Mesulam's paper was very prophetic. Nobody was thinking at the time he wrote it that amyloid and tau might be conspiring in a way that leads to microtubule disassembly."

Clutter in the Brain

Another approach to preserving the vigor of synapses focuses on the cell's ability to break down and dispose of protein debris, a process known as autophagy. Neurons, with their high metabolism, produce a lot of waste and must rely on autophagy to get rid of it. The failure of autophagy results in the accumulation of those toxic protein fragments found in Alzheimer's disease and other neurodegenerative disorders such as Parkinson's and amyotrophic lateral sclerosis (ALS), according to Ralph Nixon of the New York University School of

Medicine. "We know that this type of dysfunction develops as part of the normal aging process," he said. "We also have found that genes that promote Alzheimer's disease add another layer of impairment to this age-related impairment."

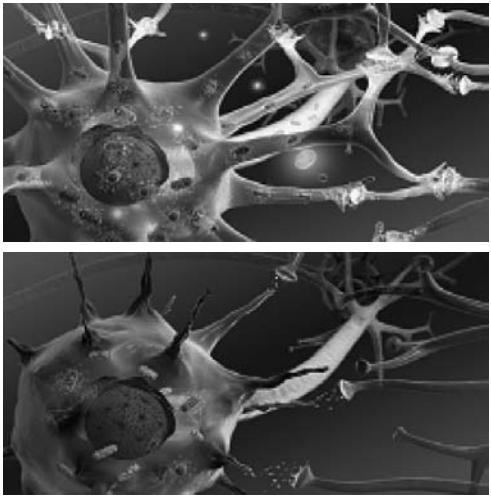
The accumulation of protein debris within the cell body plays a key role in Alzheimer's, as Nixon and colleagues outlined in a 2008 paper in the journal *Autophagy*.[13] Stimulating autophagy in the elderly presumably would slow or halt the degeneration farther upstream before amyloid plaques, tau protein tangles, and other downstream debris appear, according to Fen Jin-A Lee and Fen-Biao Gao, two researchers at the Gladstone Institute of Neurological Disease in San Francisco.[14]

Further evidence that autophagy is involved in Alzheimer's comes from Tony Wyss-Coray of Stanford University, who believes that beclin 1, a key regulator of the autophagy pathway, is reduced in certain brain areas of Alzheimer's patients.[15] When beclin 1 is reduced, neurons produce more APP, setting the stage for Alzheimer's pathology. "And beclin 1 is reduced by 60–70 percent in Alzheimer's disease," said Wyss-Coray. "Autophagy is involved in neurodegeneration in general."

Latest Avenues of Treatment

Despite these tantalizing hints that the most effective treatment for Alzheimer's would involve prevention, most treatments in the pipeline in 2008 involved removing the toxic oligomers. The antihistamine Dimebon, for example, was sold for two decades in Russia before neurologists noticed that it seemed to help people with Alzheimer's. In 2008 the conclusion of an eighteen-month study of Dimebon (dimebolin hydrochloride) showed that the drug improved memory and cognition in Alzheimer's patients somewhat, possibly by stimulating the function of mitochondria, the power source of cells.[16]

Another drug known as methylene blue, or methylthioninium chloride (MTC), has been found to inhibit the production in the brain of tau protein tangles, according to Claude M. Wischik, chairman of TauRx Therapeutics, which is marketing the compound for Alzheimer's disease under the name rember.[17] Before World War II and the widespread availability of antibiotics, MTC was sold as Urolene Blue, a treatment for urinary tract infections. A clinical trial completed in 2008 by TauRx found that the compound slowed the



Improved function of mitochondria (the small, pill-shaped structures shown with a healthy neuron, above, and with a neuron affected by Alzheimer's, below), as stimulated by experimental drug dimebolin hydrochloride, may inhibit cell death in brains with Alzheimer's disease.
(Rachelle S. Doody, M.D., Ph.D. / Baylor College of Medicine)

decline of Alzheimer's patients by 81 percent compared with patients taking a placebo.

Elsewhere, Prana Biotechnology is developing a compound known as PBT2, which interrupts the aggregation of beta-amyloid in the brain of Alzheimer's patients by inhibiting the action of zinc and copper. "The drug will keep metals away from beta-amyloid but make them bioavailable to enzymes that need them," said Rudolph Tanzi, the Harvard researcher who founded Prana in his laboratory in 1997. A clinical trial completed in 2008 showed that PBT2 reduced levels of A-beta 42—one fragment of beta-amyloid believed to be toxic to the brain—and produced some improvement in cognition.[18]

Norman R. Relkin of Weill Medical College of Cornell University is leading an effort to develop a new form of immunotherapy known as intravenous immunoglobulin, or IVIg. IVIg contains antibodies from human blood that attack beta-amyloid, but instead of recognizing the protein's chemical makeup, the antibodies recognize its misfolded, aggregated shape, and they leave healthy molecules alone. A clinical trial completed in 2008 showed IVIg capable of reducing beta-amyloid and improving cognition, opening the way for a Phase III trial.[19]

Such varied approaches underscore the complexity of Alzheimer's—and of the aging process itself. "A greater understanding of the normal aging brain may be necessary before we can fully understand the causes of pathological aging and cognitive decline," said Harvard's Bruce Yankner, who has been studying brain aging for many years.

The current amyloid cascade hypothesis leaves room for hope that the disease might be held at bay, perhaps indefinitely, by preventing

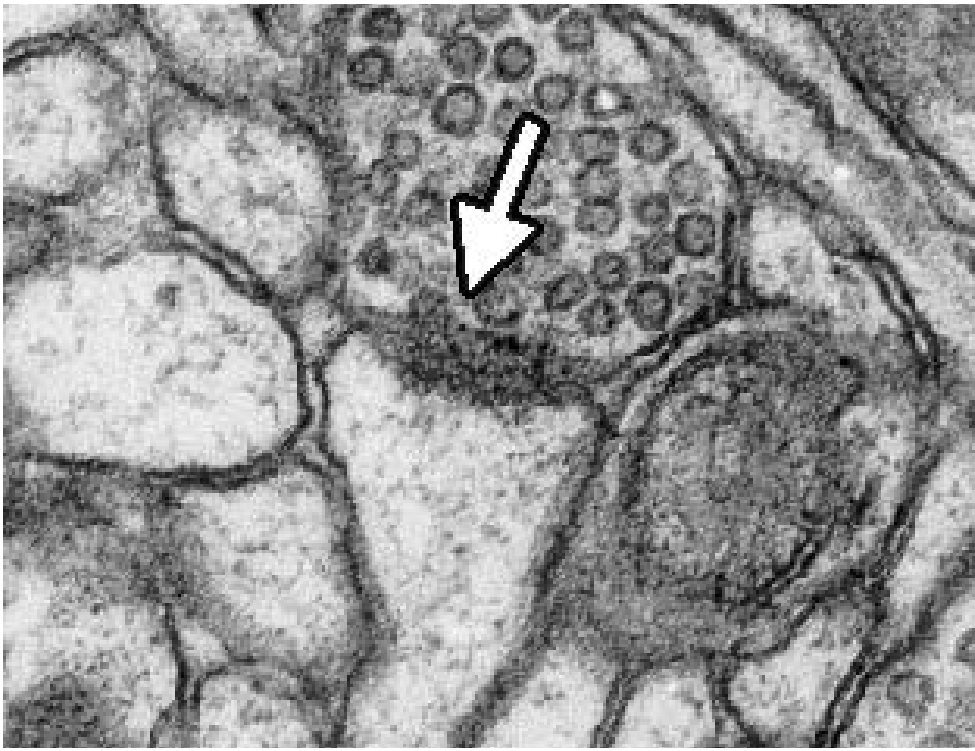
the aggregation of beta-amyloid fragments cleaved from APP throughout life. But scientists do not yet understand why the appearance of plaques does not correlate with symptoms of the disease.

Researchers will not find a "magic bullet" that cures Alzheimer's anytime soon. Toxic oligomer research may synthesize the various leading theories. Amyloid toxicity is particularly consequential when it triggers tau formation, a fact that links the amyloid cascade hypothesis to the possible pathogenic role of tau. However, scientists will need to know much more before they can conclude that such a synthesis is possible. Until then, the various hypotheses of Alzheimer's disease are still just that: hypotheses.

THE QUEST FOR BETTER SCHIZOPHRENIA TREATMENT

Serendipity and Science

Hakon Heimer



A neuron's synapse, the space between cells indicated by the arrow, before the release of small vesicles filled with glutamate, a neurotransmitter implicated in schizophrenia

(Karin Sorra, Ph.D. and Kristen M. Harris, Ph.D. / Synapse Web, Kristen M. Harris, PI)

In the early 1950s, a chance discovery helped transform schizophrenia from mystical affliction to medical disorder. French psychiatrists discovered that chlorpromazine, a drug used to make surgical patients less anxious, also relieved the symptoms of psychosis. The subsequent discovery that chlorpromazine targeted a brain messenger molecule called dopamine kicked off a large research effort into dopamine dysfunction in schizophrenia.

A half-century later, another avenue of research has yielded exciting results. Two recent studies—one a clinical drug trial and another a basic science study in laboratory mice—have helped turned the focus to a different messenger molecule, or neurotransmitter, called glutamate. In September 2007, researchers at Eli Lilly published a study showing that an experimental compound that inhibits glutamate signaling was able to reduce psychosis.[1] Although the trial awaits confirmation, and it remains to be seen whether this particular compound will be any more effective or have fewer side effects than the older drugs, the results validate the basic neuroscience research and purposeful drug development that offered up the first successful new drug target in more than half a century.

Reinforcing this new emphasis on non-dopamine causes of schizophrenia, researchers at the University of California, San Diego, reported in December 2007 that interfering with glutamate signaling in their mouse model also disrupted brain cells that use yet another neurotransmitter, this one called gamma-aminobutyric acid (GABA).[2] The fact that the GABA cell alterations mimicked those seen in schizophrenia may help to unite two prominent, and competing, theories of schizophrenia causation.

Schizophrenia Without Drugs

Although chlorpromazine (later sold as Thorazine in the United States) rescued schizophrenia sufferers from failed treatment strategies such as electroshock therapy, induced insulin shock, and frontal lobotomy, it did not restore full functionality to patients, as disabling cognitive and motivational symptoms persisted. Indeed, even today researchers are only in the infancy of understanding a disorder that was reported in historical texts as early as Pharaonic Egypt.

An important turning point in understanding psychotic disorders came around the turn of the twentieth century, when the German psychiatrist Emil Kraepelin distinguished two types of disorders

featuring delusions, hallucinations, and other thought disruptions. The major distinction between "dementia praecox" and "manic depression," Kraepelin postulated, was that although people with manic depression (now called bipolar disorder) might experience psychosis during manic periods, they return to relatively normal cognitive function when they come down from the mania. For people with dementia praecox, later termed "schizophrenia" by Kraepelin's countryman Eugen Bleuler, psychosis is an ongoing state, often accompanied by profound deterioration in the ability to process information or interact socially.

The modern diagnosis of schizophrenia requires the persistence of psychotic, also called "positive," symptoms for at least six months, without evidence of mood cycling. However, psychosis is not the only symptom of schizophrenia. Most people with the disorder also exhibit poor working memory (information stored temporarily during a task) and are unable to quickly recognize new situations and rules, an ability termed cognitive "flexibility." These cognitive features contribute greatly to the chronic disability of most patients, as does a third symptom domain, that of "negative" symptoms. Negative symptoms describe aspects of normal behavior that are subtracted by the disease process—typically motivation, the display of emotion, or the desire to interact with other people. Thus, the most severely afflicted find themselves in a constant state of confusion about the events going on around them, without the capacity to have normal social interactions.

The Chlorpromazine Puzzle

The work of the German classifiers and their contemporaries had no direct benefit for people with schizophrenia and other psychotic disorders. Indeed, the next half-century saw some horrifically misguided attempts to alleviate the suffering of patients and their families. Treatments such as the surgical disconnection of major brain pathways with frontal lobotomy were the result of physicians' moving forward with slim scientific evidence.

Finally, in the second half of the twentieth century, antipsychotic drugs provided a logic and a strategy for looking for chemical or structural changes in the brains of people with schizophrenia. If a single molecule—chlorpromazine—could reduce and in some cases eliminate the complex manifestations of schizophrenia, then it stood

to reason that there was a chemical imbalance in the brain.

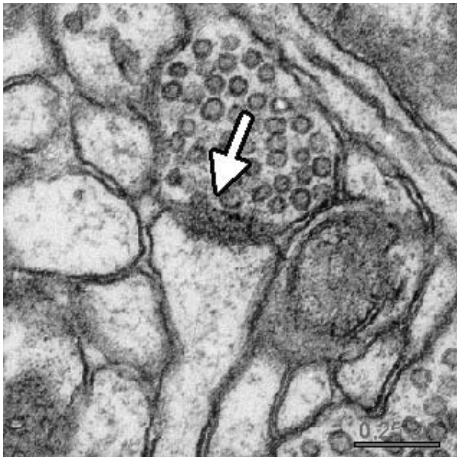
The Swedish scientist Arvid Carlsson had discovered dopamine in the early 1950s, and a decade later he and his colleagues determined that antipsychotic drugs worked by blocking dopamine from attaching to its receptor molecules. This finding dovetailed with another serendipitous finding: as early as the 1930s, it had been noted that amphetamine could cause psychosis. Amphetamine and other psychostimulants, it turns out, boost the activity of dopamine. Thus, the "dopamine hypothesis" of schizophrenia was born.

For the next several decades, researchers focused on trying to understand how dopamine systems were disturbed in the disorder. However, despite some significant refinements to chlorpromazine, especially reductions of some side effects, this line of research has been disappointing. According to Joseph Coyle of Harvard University, one of the first schizophrenia researchers to turn their attention to glutamate, 70 to 80 percent of patients with schizophrenia treated with dopamine drugs remain profoundly impaired by cognitive and negative symptoms. Moreover, neither a clear understanding of how blocking dopamine receptors curbs psychosis nor any new molecular targets have emerged from this line of research. Most psychiatry researchers are currently of the opinion that the dysfunction of dopamine neurotransmission in schizophrenia results from, or compensates for, a more fundamental or "upstream" disturbance of the nervous system, perhaps in glutamate signaling.

The Biggest Little Neurotransmitter You've Never Heard Of

While the public has had many opportunities to learn about the important role of dopamine in the brain, especially in regard to Parkinson's disease and the rewarding effects of sex, drugs, and chocolate, glutamate remains relatively unknown. In fact, it is the most common neurotransmitter in the brain and the signaling molecule of choice of the powerful pyramidal neurons. So named for their shape, these cells send information shooting around the cerebral cortex and other brain areas that control behavioral functions, rapidly combining sensory input with stored information and emotions.

One reason for glutamate's anonymity in the public mind is that its status as a neurotransmitter was demonstrated only some twenty years ago. Researchers had long known that it was abundant in the brain,



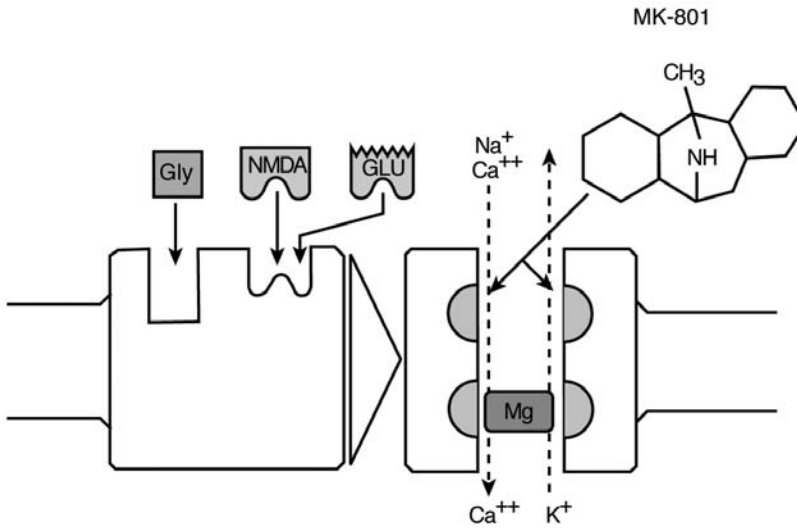
At the end of an axon, round vesicles containing glutamate await an electric charge from the cell body. The glutamate molecules will be released into the synapse, the fuzzy space separating the axon from a neighboring cell, indicated by the arrow.
(Karin Sorra, Ph.D. and Kristen M. Harris, Ph.D. / Synapse Web, Kristen M. Harris, PI)

but it is involved in numerous other cell activities as well. In order to qualify glutamate as a true neurotransmitter, scientists had to establish that it was released by nerve cells at the ends of long fibers called axons. Researchers also showed that glutamate, like dopamine and all other neurotransmitters, crosses a narrow space beyond the axon called the synapse and binds to receptor molecules on the surface of other neurons, triggering rapid electrical or chemical activity in the second cell.

Once scientists had established the status of glutamate, especially in the cortex, they were quick to explore the possibility of glutamate dysfunction in schizophrenia. Here another bit of serendipity came into play. As with amphetamine and the dopamine hypothesis, it involved a drug that caused psychosis.

Remarkably, the drug phencyclidine was another gift from the anesthesiologists. Developed as an anesthetic in the 1950s, phencyclidine (PCP, called "angel dust" as a street drug) was soon pulled from regular use because it caused psychotic symptoms during recovery. But whereas amphetamine produces only the positive (psychotic) features of schizophrenia, PCP and chemically similar anesthetics such as ketamine produce both negative and cognitive symptoms as well. David Lodge and colleagues at the University of London supplied the link to glutamate in 1983, when they found that PCP and ketamine bind to one particular type of glutamate receptor called the N-methyl-D-aspartate (NMDA) receptor.

Researchers soon began to advance theories about how glutamate dysfunction might play a role in schizophrenia, led by Daniel Javitt of the Nathan Kline Institute in New York in 1987, as well as Joseph



Activation of the N-methyl-D-aspartate (NMDA) receptor occurs when either glutamate (Glu) or NMDA and glycine (Gly) bind to the receptor molecule, shown on the left. A channel within the receptor complex enables molecules to cross the cell membrane. Magnesium (Mg) blocks this channel. When Mg is removed from the channel and the receptor is activated, calcium (Ca++) and sodium (Na+) ions enter the cell and potassium ions (K+) leave.
(J.D. Thomas and E.P. Riley / NIH National Institute on Alcohol Abuse and Alcoholism)

Coyle and his colleagues and John Olney of Washington University in St. Louis. If PCP and ketamine produced a schizophrenia-like state by interfering with normal NMDA receptors, then perhaps these receptors were performing poorly in the disorder. Evidence emerged from studies of postmortem brain tissue—some, but not all, such studies have found modest evidence of alterations in glutamate-related molecules in the brains of people with schizophrenia. The glutamate hypotheses have also gained support from genetic research—among the genes that have the strongest support as schizophrenia susceptibility candidates are several that code for proteins that influence glutamate signaling. In particular, a meta-analysis of genetic studies, by Lars Bertram and colleagues at Massachusetts General Hospital and published in 2008, found that variation in one of the subunits that makes up the NMDA receptor increases the risk for the disease.[3]

Researchers, particularly Javitt and Coyle, have conducted clinical trials to boost the function of NMDA receptors. Although negative and cognitive symptoms improved in these small preliminary trials, the results were not strong enough to induce the pharmaceutical

industry to pursue drug development efforts. However, a breakthrough at the turn of the new millennium has led to a revitalizing of these approaches.

A Different Window onto the Glutamate Synapse

While Coyle, Javitt, and others were focused on modulating the NMDA receptor directly, Bita Moghaddam at Yale University had turned her attention to a different class of glutamate receptor. Called metabotropic glutamate receptors (mGluRs), they do not rapidly convey information at glutamate synapses, as NMDA receptors do. Rather, they influence how the glutamate synapse operates in various and subtle ways. In a paper published in 1999, Moghaddam and colleague Barbara Adams took advantage of the fact that PCP and other NMDA-interfering drugs can be used in animal models, where they produce effects strikingly like the negative and cognitive symptoms of schizophrenia patients.[4] When they gave rats a drug that activates only mGluRs, the researchers found that the cognitive effects of PCP—e.g., working memory impairment—were significantly reduced. In 2005, John Krystal of Yale University and his colleagues replicated this finding in humans, showing that the same mGluR receptor drug could reverse the cognitive effects of ketamine in healthy volunteers.

These studies set the stage for Eli Lilly to try the mGluR drug in people with schizophrenia. As the Lilly researchers reported in their 2007 paper in *Nature Medicine*, in a double-blind, placebo-controlled trial conducted in Russia with nearly 200 patients, they found that the experimental drug was significantly better than the placebo in treating positive symptoms, the first non-dopamine blocker to achieve this distinction.[1] They did not report on whether they had found effects on cognitive measures, as Moghaddam and Krystal had in their experiments. The study is now being repeated in a different group of patients, with different doses of the mGluR drug. The Lilly trial provides not just proof of concept evidence for the target, but also proof of concept evidence that the strategy can yield new drugs that may turn out to be effective, according to David Lewis of the University of Pittsburgh's Western Psychiatric Institute, one of the researchers who had demonstrated changes in glutamate-related molecules.

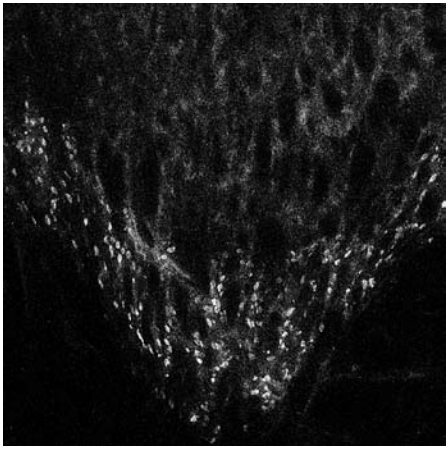
It's Not All Excitatory

Another significant glutamate study published in 2007 pointed out both the significant advances and the remaining challenges in understanding schizophrenia pathology. Margarita Behrens, Laura Dugan, and their colleagues at the University of California, San Diego, reported in *Science* that interfering with glutamate NMDA signaling in mice can reproduce one of the most well-supported findings in schizophrenia: disruptions of cells called interneurons, which signal using the neurotransmitter GABA.[2]

GABA is the yin to glutamate's yang. While glutamate is the neurotransmitter of choice for the pyramidal neurons, which use it to excite electrical activity in the neurons they contact, GABA is typically employed by a more modest group of cells, the interneurons. These cells confine their axons to their local areas, in which their bursts of GABA inhibit the activity of the pyramidal neurons. Researchers including David Lewis, Francine Benes at McLean Hospital in Belmont, Massachusetts, and others have found changes in GABA-related proteins in schizophrenia but only in a select population of interneurons. A recent study in genetically altered mice also points to GABA cell problems in schizophrenia. Akira Sawa and colleagues inserted a mutant form of the schizophrenia susceptibility gene called "disrupted in schizophrenia 1" (DISC1) into mice.[5] When they examined the brains of the mice, the researchers found that the same interneurons affected in schizophrenia are altered in the mice with mutant DISC1. The researchers described their work in a 2007 paper in *Proceedings of the National Academy of Sciences*.

Lewis and his collaborators are now testing a drug that may normalize GABA interneuron function in the brain of people with schizophrenia, perhaps with a beneficial effect on symptoms.

However, Behrens, Dugan, and colleagues' intriguing finding is that the NMDA blocker ketamine selectively damages this same group of GABA interneurons. The researchers suggest that the glutamate deficit might therefore be "more primary," or "upstream" of the GABA deficit. The intermediate step, their report suggests, may be the production of destructive molecules called "free radicals." These results have not been confirmed, so the conclusions vis-à-vis schizophrenia remain speculative. But in 2008 Behrens, working with John Lisman of Brandeis University, added supporting evidence for the link between glutamate and GABA disruptions.[6] As they reported in the



Margarita Behrens and colleagues found that abusing ketamine, which inhibits the NMDA receptor, can result in symptoms indistinguishable from schizophrenia in the mouse prelimbic cortex. At right, ketamine has reduced the expression in the prelimbic cortex of parvalbumin (the large, light-colored spots), a molecule reduced in GABA cells in schizophrenia.
(M. Margarita Behrens, Ph.D. / University of California, San Diego)

Journal of Neurophysiology, they were able to directly record altered electrical activity in GABA interneurons that had been disrupted with an NMDA receptor blocker.

Searching Between Drugs and Behavior

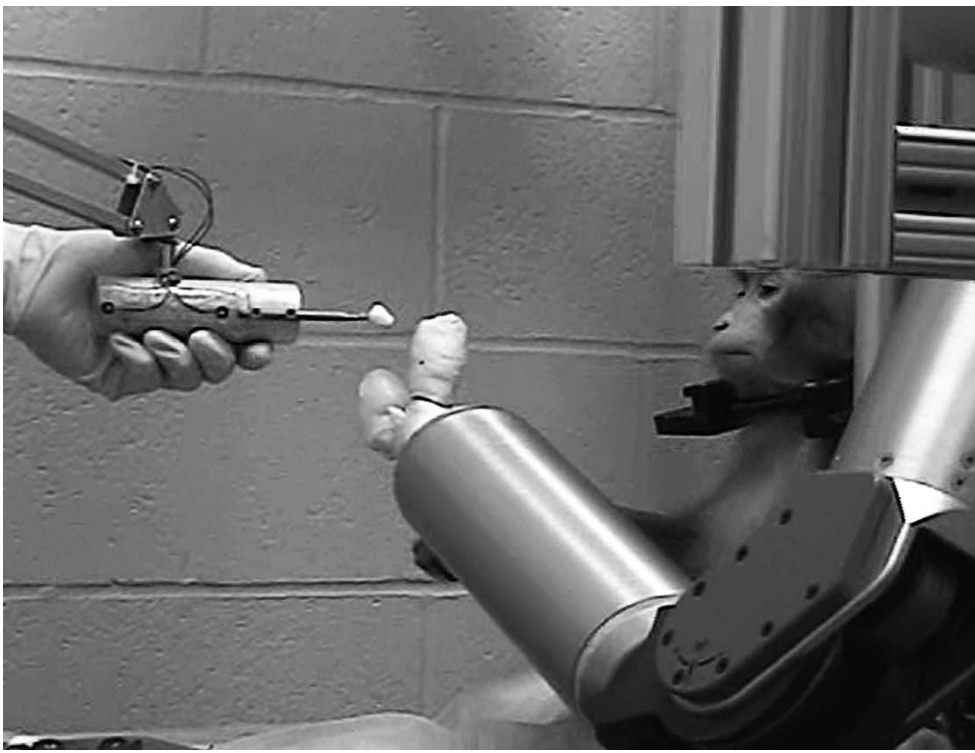
The results of Behrens and colleagues highlight the need to work out the complex set of relationships between the different types of neurons in the brain, said Coyle. The strategy of giving different compounds to animals or people and studying how their behavior changes, which has been so productive in the case of the NMDA-blocking drugs, still leaves a fuzzy area between the drug input and the behavior output. In addition to the ongoing debate on the relative importance of glutamate versus GABA disruption in schizophrenia, researchers disagree on whether the neurons of most interest are those in the higher-reasoning areas of the cortex, in areas that connect the cortex with sensory or movement regions of the brain, or both.

Scientists will now attack the neuronal circuits from different entry points: they will explore metabotropic glutamate receptors (of which eight variations have been identified), as well as the manipulation of other glutamate receptors and molecules that help control the amount of glutamate floating about in synapses. Researchers will also focus

on the cells on the receiving side of glutamate neurotransmission, principally the GABA interneurons and their connections back to the glutamate-releasing pyramidal cells. Other neurotransmitters, such as dopamine, acetylcholine, and serotonin, will receive attention because they subtly alter communication between glutamate and GABA cells. It remains to be seen whether any single approach will lead to a drug that effectively treats schizophrenia, or whether different compounds, targeting separate neurotransmitter systems for the different symptom domains, will be needed.

BRAIN-MACHINE INTERFACES
Sci-fi Concepts Make Clinical Inroads

Brenda Patoine

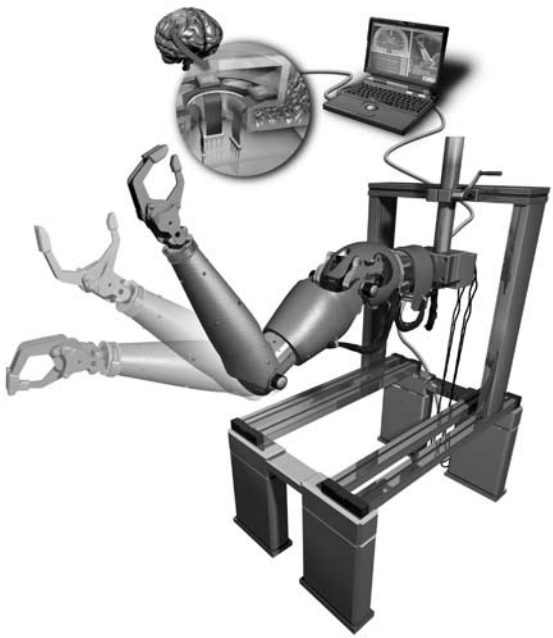


A monkey feeding itself using a robotic arm controlled by brain signals at the University of Pittsburgh
(Andrew B. Schwartz, Ph.D. / University of Pittsburgh)

A woman in a Boston suburb, "locked in" from a brain-stem stroke for more than a decade, checks her e-mail using thoughts alone to command the computer. In a laboratory in Pittsburgh, macaque monkeys learn to feed themselves marshmallows using a thought-controlled prosthetic arm, adapting and refining its movements as if it were their own appendage. In North Carolina, researchers capture the thoughts of a twelve-pound monkey and transmit them to Japan via high-speed Internet to make a two-hundred-pound humanlike robot walk, apparently the first instance on record of such remote transmission.

Thought-controlled robotics and computers commanded by neural activity recorded directly from the cortex are no longer strictly the province of science fiction; they are here and now. Recent advances have propelled the young field of "neural prosthetics" forward. As researchers work on the details required to take "brain-computer interfaces" into clinical practice, they have an ambitious vision: to restore mobility or communication to patients with severe neurological damage from brain disease or injury.

To date, four human patients have been fitted with brain-computer interfaces—also variously called neural prosthetics, neural interfaces, or brain-machine interfaces. All four have participated in a pilot clinical trial investigating a neural interface called BrainGate. The system



Scientists have shown that brain waves can move a robotic arm purposefully. In a study testing this concept, macaque monkeys learned to perform a self-feeding task.
(Andrew B. Schwartz, Ph.D. / University of Pittsburgh)

is being developed by Cyberkinetics, Inc., a small company founded by Brown University neuroscientist John P. Donoghue.

Leigh R. Hochberg, a neurologist at Massachusetts General Hospital/Harvard Medical School and the trial's principal investigator, said in August that one person is currently enrolled, a 54-year-old woman who suffered a stroke in the brain stem twelve years ago, which left her immobilized from the neck down and unable to speak. Using the BrainGate interface, the woman, whose name has not been revealed publicly, has learned to control a computer cursor to conduct rudimentary functions, including opening her e-mail and turning on a television or lights. She has also successfully moved an electronic wheelchair, albeit not while in the chair, using only her intention to do so.

Hochberg said his team worked with her over a thirty-month period in weekly sessions lasting up to eight hours each. Even early in the process, he said, she had achieved "fairly reliable and rapid control of the cursor." The latest results from the trial were presented at the 2008 Society for Neuroscience meeting in November. "There are some things that we can only learn through regular feedback from the patient," Hochberg said. "This woman is teaching us a lot."

Of the three other patients who have been enrolled in the BrainGate trial, two had the device removed after a year—an option that is built into the trial. Both were quadriplegic (paralyzed in all four limbs) following spinal cord injuries at the cervical level. A fourth patient, who had amyotrophic lateral sclerosis (ALS), died after ten months with the interface, due to a ventilator problem apparently unrelated to the brain prosthetic, Hochberg said.

Proof of Principle

Studies in patients with severe disabilities have provided proof of principle that neural interfaces can work, even in people who have been completely immobilized for many years. But the BrainGate interface, while far and away the farthest along in clinical development, is a long way from the ideal. Even its lead developer, Donoghue, has conceded that the system as it exists now is cumbersome and impractical—primarily because of the large banks of equipment necessary to decode the neural signals into useful commands and the thick wad of cables tethered to the patient's skull that links the interface to the equipment. Still, by all accounts it is an impressive demonstration of what is possible.

"It's important to remember that these are individuals who are otherwise locked in," said William Heetderks, a National Institutes of Health scientist who headed the federal government's neural prosthetics research program for many years. "The neurons being recorded from have not been used to generate movement for many years, in most cases. When you think of it that way, it's kind of amazing that this works at all."

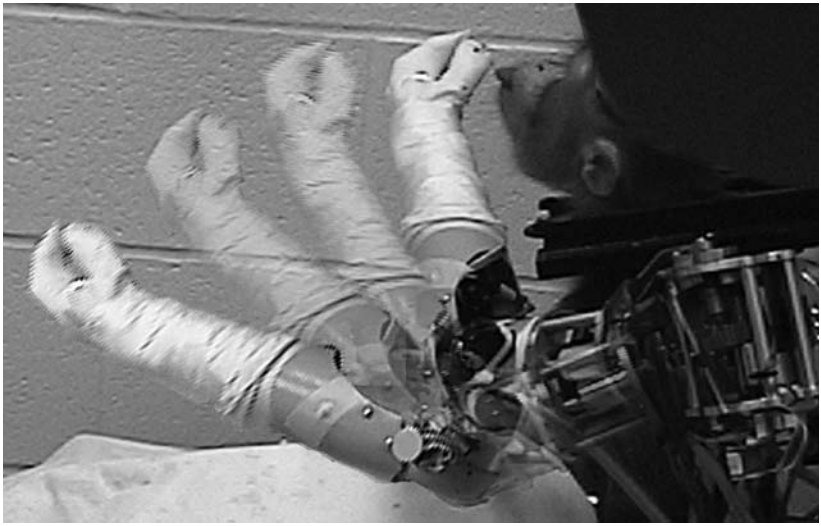
The first results of the BrainGate trial, from a 25-year-old quadriplegic man who has since had the device removed, were reported at the neuroscience meeting in 2004 and later published in *Nature*.[1] When the early results were made public, many people balked at the notion of implanting electrodes in the cortex and questioned whether the technology had been adequately studied in animals before human experiments commenced. Such questions persist.

"There will always be this issue of when is it ready to go into humans," Heetderks said at the time. "If you waited until everyone agreed the time was right, it wouldn't happen for a long time. I think the data supporting putting electrodes into humans was strong and fairly convincing in terms of being safe and realistically having a very good chance of working. Obviously, the FDA was convinced," he added, since the agency approved the trial.

Monkey Think, Monkey Do

As the BrainGate trial continues to enroll patients, other researchers in the forefront of the field are focused on ever more elaborate demonstrations of the utility of neural prosthetics in nonhuman primates. One of the latest reports, published online in *Nature* in May 2008, came from the University of Pittsburgh laboratory of Andrew B. Schwartz, one of the field's pioneers.[2] In what the *New York Times* called "the most striking demonstration to date of brain-machine interface technology," Schwartz's group trained two monkeys to control an advanced anthropomorphic robotic arm, complete with shoulder and elbow joints and a clawlike gripper serving as a hand.[3]

The researchers had implanted into the monkeys' primary motor cortex the same kind of electrode grid used in the BrainGate trial, which records signals from about one hundred neurons in the motor cortex. They then trained the animals to generate patterns of brain activity to move the robotic arm in three dimensions. With their own arms gently restrained and the prosthesis positioned near their



A monkey feeds itself during a three-dimensional brain control task. In this experiment the monkey controlled the velocity of the arm's endpoint. In subsequent experiments, the monkey also controlled the opening and closing of the arm's grip. (Andrew B. Schwartz, Ph.D. / University of Pittsburgh)

shoulder, the monkeys learned, after only a few days, to smoothly and naturally reach the arm out to a piece of fruit or a marshmallow, open the gripper and remove the treat from its peg, return the treat to their mouths, and open the gripper to release the food. Even more remarkably, the monkeys learned to adapt the movements of the robotic arm, adjusting its movement, for example, when a marshmallow became stuck on the gripper or when the researchers changed the location of the treat.

In an editorial accompanying the *Nature* paper, John F. Kalaska, a neurophysiologist at the University of Montreal, called the work "the first reported demonstration of the use of [brain-machine interface] technology by subjects to perform a practical behavioral act—feeding themselves," and said it represents the "current state of the art in the development of neuroprosthetic controllers."[4]

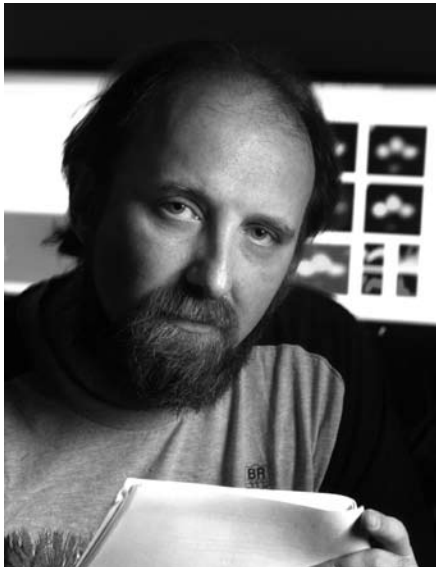
'Real-World' Demonstration

To Schwartz, the primary significance of the report is that "the animal is working in the real world. Up until now, there have just been demonstrations of subjects moving a cursor on a computer screen. Our research shows that this can work in three dimensions, not just two." (Three-dimensional movement would enable a patient to have

far greater capacity for performing basic functions of daily living, such as eating.)

The most recent reports build on previous research in primates, including a 2003 paper by Miguel Nicolelis's laboratory at Duke University demonstrating that a monkey could be taught to use brain activity to move a disembodied, rudimentary robotic arm, the first published report of a primate reaching and grasping with a robotic arm via a neural interface.[5]

In work not yet published but reported in January 2008 by the *New York Times*, Nicolelis's group demonstrated for the first time that a monkey's brain signals could make a robot located on the other side of the world walk.[6] The researchers recorded the monkey's neural signals as it walked on a treadmill, then decoded the signals and transmitted them to a laboratory in Japan, where they were fed into an advanced robot that mimics human locomotion. When the monkey walked, so did the robot, and the monkey was able to see the effects on a large-screen video monitor placed in front of her, providing critical visual feedback. The robot's movement precisely mimicked the monkey's, according to the news report. After an hour or so, the researchers stopped the monkey's treadmill. The robot kept walking. Apparently, a subset of the monkey's neurons had "adopted" the robot's leg movements as the monkey's own movements, and encouraged by tasty rewards, the monkey had learned to keep the robot moving.



Miguel Nicolelis and colleagues at Duke University taught monkeys to use brain signals to control the movements of a robot on the other side of the world. The researchers trained some of the monkey's neurons to "adopt" the machine's locomotion as its own.
(Miguel Nicolelis, M.D., Ph.D. / Duke University)

Fantastical as it may seem, the concept behind such demonstrations is fairly straightforward: record electrical activity from the right set of neurons and translate the signals, via sophisticated mathematical algorithms, to power external devices—be it a computer cursor, a prosthetic limb, or a wheelchair. In reality, of course, executing the concept is anything but simple. It has taken decades of concerted effort by a small but growing group of researchers to advance neural interface technology from a pie-in-the-sky concept to here-and-now reality.

The NIH neural prosthetics program, now in its fortieth year, nursed the young field along by funding many of the research groups now in the forefront. A piece of this program was aimed at doing precisely what has now been done: use neural signals recorded from the cortex to control an external device.

"When we started this, we asked what would constitute a minimum demonstration of feasibility," Heetderks said. "We decided that one-dimensional control was a reasonable place to start." The most recent results by Schwartz's group "are more elegant than we had imagined," Heetderks said, because they extend movement into three-dimensional space, which allows natural, fluid movement.

Basic Research Laid Groundwork

The latest advances build on decades of basic science research aimed at unraveling the function of the brain's motor cortex, where movements are initiated and carried out, and relating specific neuronal populations to movement direction and velocity. In the early 1970s, Eberhard Fetz, now at the University of Washington, Seattle, and colleagues demonstrated that monkeys could be trained to increase or decrease their cortical activity to move a device akin to a radio dial up or down, work that Hochberg called "instrumental" in proving the principles behind today's neural prosthetics. In addition, basic research in the 1980s by Schwartz and his mentor, Apostolos Georgopoulos, a cognitive neuroscientist now at the University of Minnesota, had demonstrated that it should be possible to get "good three-dimensional control" of external devices by recording from as few as fifty or sixty neurons in the motor cortex, Heetderks said.

Largely as a result of the strength of such basic research, Heetderks said, "There was never really any question that this was possible, in principle." Rather, the question was "how much information do you have to pull out of the brain to make precise movements?"

The advent of cochlear implants for the hearing-impaired, first developed in the 1960s and used today by more than 100,000 people, has provided critical proof of principle that it is possible to alter sensory function by targeting a relatively small number of neurons. The devices are composed of a tiny external headpiece and processor that pick up sound waves and convert them into digital signals that are then transmitted through the skin to the implant, which is attached to the skull inside the ear. The signals activate electrodes within the cochlea, a critical organ in the brain's hearing machinery, to stimulate neurons connected to dysfunctional inner-ear cells called "hair" cells, which normally transmit sounds to the brain.

"It is difficult to overestimate the importance of the cochlear implant to the development of neural prosthetics," said Heetderks, pointing out that early versions of the cochlear implant used only four stimulating electrodes, while modern models use about twenty. "Thirty years ago, I would have said it won't work: how could you possibly represent all the richness of sound with just a few stimulating electrodes?

"The fact that it worked shows how remarkable the brain is at interpreting scrambled information," Heetderks added. "It made believers out of doubters."

Meeting the Challenges Ahead

As the young field of neural prosthetics marches forward, several key challenges remain. In particular, experts cite the need to improve the long-term reliability of the implanted electrode arrays that are used to record neural signals. The current participant in the BrainGate trial has had her implant in place for nearly three years, and while it has continued to operate throughout that period, the researchers have seen fluctuations of unknown cause in the richness of the signals, according to Hochberg. Researchers are also concerned about the "foreign-body response" of immune cells to electrodes chronically implanted in the brain, he said. "It's clear that we have to improve the recording stability, either by changing the material or the surgical methods used for implanting the electrodes."

Richard A. Andersen, a neurobiologist at the California Institute of Technology with expertise in optimizing signal-recording methods for neural prosthetics, doesn't think that "recording longevity," as he terms it, is a significant limitation for the field. "If the electrodes are well-made

and durable, it appears that they can last for years," he said.

Researchers also hope to make the neural interface systems more practical for human use. Development of a wireless interface is critical, to obviate the need for cables running from the brain implant to the decoding hardware. The challenge there, according to Andersen, is to develop an implant that has a built-in power source and is sufficiently low-powered that it will not heat up brain tissue, which could cause serious problems. A number of groups are working to overcome this hurdle, which requires developing a fully implantable electrode array with integrated electronics, a power source, and high-resolution signal transmission. Donoghue's group at Brown, for example, is developing a fully implantable neuromotor prosthetic "microsystem-on-a-chip," which incorporates advanced ultra-low power microelectronic circuits and processors. Fiber-optic technologies are also being exploited as a means to provide both a power source and efficient signal transmission.

Scientists continue to debate which neural signals to capture to achieve the best results. The BrainGate system and the systems used by Schwartz and Nicolelis in the most recent advances target a discrete population of neurons in the motor cortex—an appealing target because of the long history of solid basic research delineating the precise actions of these cortical motor neurons. But other targets may afford advantages also. Andersen's team has focused on a part of the parietal cortex involved in reaching movements.

Recording from neurons in this "reach region" of the parietal cortex provides higher-level signals related to the goals of movements—the stage just before a motor command is issued. Andersen said targeting these signals has the advantage of enabling the decoding of a wide variety of cognitive signals, which opens new possibilities for using neural prosthetics for a range of cognitive functions well beyond movement. For example, it might be possible to record thoughts from speech areas to facilitate communication in locked-in patients. In the distant future, electrodes may record from multiple regions of the cortex to drive a potentially unlimited range of cognitive functions.

Despite the challenges, researchers in the trenches of this field are optimistic. "I don't see any major insurmountable challenges to moving the field forward," said Andersen.

Schwartz echoes this sentiment: "Most of the challenges that remain are not earth-shattering, but rather mundane problems. There is nothing here that a concerted effort can't address."

A concerted effort to take neural prosthetics to the next level is precisely what the Defense Advanced Research Projects Agency (DARPA) has in mind with its "Revolutionizing Prosthetics" initiative. With a budget of nearly $50 million over six years, the military-funded project focuses multiple research centers on the goal of producing an advanced neural-controlled prosthetic arm that allows the user the full function and capability of a normal human arm—ideally to allow the user enough fine-motor control to thread a needle or play a piano. DARPA expects to begin clinical trials to test the brain-to-arm interface system in 2009.

THE OBESITY PROBLEM
When Our Hormones Betray Us

Scott Edwards

Staff members performing an in-scanner obesity experiment at the Program for Imaging and Cognitive Sciences lab at Columbia University
(Joy Hirsch, Ph.D. / Columbia University)

Research during the past two decades has raised public awareness of the brain's role in regulating how much food we eat, but our current picture of appetite and food intake emerged much earlier, when in the 1950s nutritionist Jean Meyer discovered that glucose levels in the blood regulate hunger. Meyer went on to study obesity, which he called a "disease of civilization," and he helped to link excess weight to other substances in the blood and to structures in the brain.

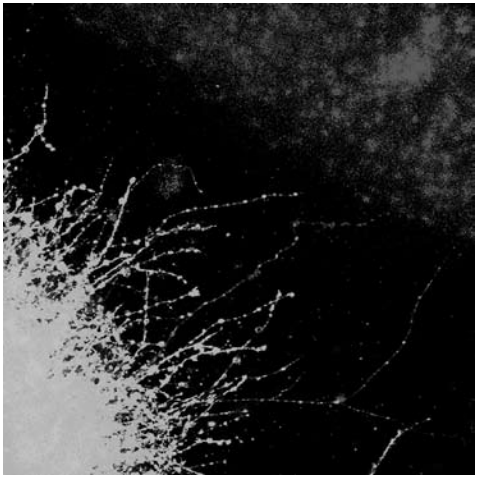
Neuroscientists have since taken up Meyer's fight. In 2008, researchers reported findings that provide a greater understanding of the role of two (out of a dozen or so known) important appetite-related hormones, ghrelin and leptin. Researchers also determined how a popular class of anti-obesity drugs can affect brain wiring and found evidence of a potential link between obesity, diabetes, and Alzheimer's disease.

The Basics of Appetite

The U.S. Centers for Disease Control and Prevention designates the labels "obese" and "overweight" for ranges of weight greater than what is generally considered to be healthy for a given height. Body-mass index, or BMI, measures body fat based on a person's height and weight. Clinicians consider a BMI of 25–29 to be overweight, while anything over 30 is obese.

Meyer helped to identify the brain's hypothalamus as a regulator of appetite, but that brain structure influences a number of other bodily functions as well, including body temperature, blood pressure, and fluid and electrolyte balances. A collection of neurons in an area of the hypothalamus called the arcuate nucleus coordinates our need to eat in relation to how well our body is fed via cross talk with signals arising from the gastrointestinal system and adipose (fat-storing) tissue. Two specific neural circuits within the arcuate nucleus promote or suppress appetite, regulating our body's nutritional state and helping to provide balance to our body weight, respectively.

In addition to the hypothalamus, the brain's limbic structures and reward circuitry contain information on food preferences acquired over our life span based on aspects such as taste and smell. Our sensory organs send food-related signals to the brain that release dopamine, a neurotransmitter that plays an important role in motivation and reward. More than food itself, our expectations—what



In a study of neural connections between brain regions, neurons from the arcuate nucleus (bottom left), which has been linked to appetite control, extend axons toward the paraventricular nucleus (top right). (Sebastian Bouret, Ph.D. / University of Southern California)

we associate with certain tastes and smells—cause the secretion of dopamine. Thus, eating really starts in our brain before we even put food in our mouths.

Several factors contribute to the world's obesity epidemic. A growing number of people find themselves unable to defy the desire to eat more food than is healthy. While many of us know that the food we eat adds inches to our waistlines, some people cannot control themselves at the dinner table. And despite spending countless hours and millions of dollars on diets and weight-loss products and services, many people lose weight only to gain it again.

Leptin and Ghrelin: Two New Players in a Large Arena

Research on appetite control in the 1970s and 1980s focused on two neurotransmitters, norepinephrine and serotonin. Both are messenger chemicals that travel across the synaptic gap between neurons. Doctors prescribed amphetamines to enhance the release of norepinephrine and thereby control appetite, and targeted serotonin for its role at the hypothalamic control centers for appetite. However, the discovery of two important hormones in the 1990s led to a finer understanding of how appetite is controlled and how, when something goes awry, obesity can occur.

In 1994 Rockefeller University researcher Jeffrey Friedman and his colleagues published a landmark paper in *Nature* that identified a hormone called leptin (Greek for "thin") produced by the obese (ob)

gene.[1] Leptin is made by the body's fat cells, which help to regulate food intake and energy expenditure (the amount of calories we burn). Friedman showed that mice lacking the ob gene do not produce leptin and become extremely obese. After both normal and ob-deficient mice were injected with synthetic leptin, they became more active and lost weight.

High levels of leptin activate nerve cells in the brain and create a feeling of fullness, while low levels signal hunger. Friedman also showed that humans who lack the ob gene and eat large amounts do not experience that feeling of fullness and end up extremely obese.

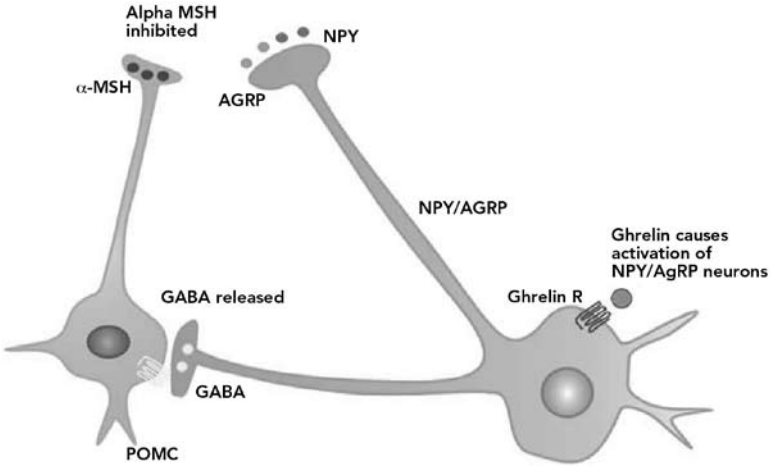
Five years after Friedman's discovery, Japanese researchers identified another hormone, ghrelin, which they called the "hunger hormone." Ghrelin is made in the stomach and tells our brain when it's time to eat. Ghrelin levels rise just before mealtime and fall after we eat.[2]

These two hormones played an important role in 2008 research aimed at discovering how to regulate food intake in obese and overweight people.

In 2007, researchers at Harvard Medical School developed what they call a "right brain hypothesis" for obesity. The right hemisphere of the brain's prefrontal cortex (PFC) plays a critical role, they say, in the cognitive control of food intake, which refers to our capacity to process information and make decisions regarding what we eat. The PFC controls a number of complex behaviors that separate humans from other species.

The Harvard researchers say that a certain amount of activity in the right PFC is required to control appetite. While the PFC is not damaged in obese people, they say, activity in this area of their brains is diminished. In addition, the right PFC is critical for what the researchers call "moral cognition," our ability to give values to different foods, which influences our decisions about what we eat. Dysregulation of the right PFC, the Harvard researchers say, could lead to inappropriate conclusions about food choices, which could contribute to obesity.

As more research supports hypotheses that emphasize the involuntary processes that lead to obesity, many scientists now view addiction as a potential contributing factor to our growing waistlines. Research studies are currently under way to examine the underlying psychology and biology behind this hypothesis. Some of these studies have focused on the neurotransmitter dopamine, which plays a role in the brain's reward circuit. In 2001, researchers at Brookhaven National



In the arcuate nucleus, the messenger chemical ghrelin, known as the "hunger hormone," activates certain types of neurons (labeled NPY and AgRP in this image). These neurons release the neurotransmitter GABA, which inhibits the release of another chemical, Alpha MSH, which in turn inhibits appetite. Ghrelin also increases appetite by causing certain neurons to release AgRP, a chemical that prevents Alpha MSH from activating its receptors. (Diabesity / www.diabesity.eu)

Laboratory reported that obese people have fewer receptors for dopamine than people without weight problems, implying that obese people may eat more to try to stimulate dopamine pleasure circuits in their brains, just as drug addicts do by taking drugs.[3] Others, however, believe that factors such as poor eating habits, lack of exercise, and genetics contribute more to overeating than do either physical or psychological dependence.

In 2008, scientists at Eli Lilly and the University of Texas Southwestern Medical Center independently discovered an enzyme that is responsible for putting a fatty acid on ghrelin, the so-called hunger hormone.[4, 5] Without this fatty acid, ghrelin might not have the same effect on appetite. The identification of this enzyme, called GOAT, or ghrelin O-acyl transferase, is the first step toward developing medications to treat obesity.

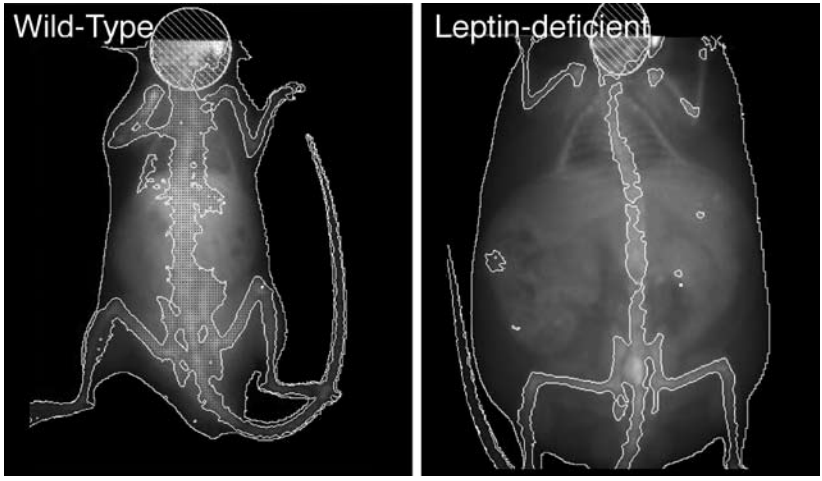
Ever since ghrelin was discovered, scientists have sought ways to manipulate the hormone to help tame hunger. With the discovery of GOAT, researchers are now testing compounds that block the enzyme from attaching to ghrelin. One promising approach uses antibodies to sop up the enzyme and block ghrelin signals to the brain.

Hardwired to Be Obese?

In February 2008, researchers at the University of Southern California showed that a predisposition to obesity might be hardwired in the brain at birth.[6] The researchers selectively bred rats that were prone to becoming obese and found that the regions of their brains that control appetite were abnormal. The arcuate nuclei of the obese rats were defective, leaving their brains less receptive to leptin, a hunger-suppressing hormone. These abnormalities showed up in the mice as early as the first week after they were born.

Under the direction of Sebastien Bouret, the USC researchers discovered that the obesity-prone rats had fewer neural projections from the arcuate nucleus, a problem that continued into adulthood. These projections enable leptin to signal from the arcuate nucleus to other parts of the hypothalamus. Bouret's team said that appetite and obesity are built into the brain during development and that the propensity to gain weight cannot be reversed. Scientists are trying to determine how to treat this abnormality during early, critical phases of development by rewiring the brain so that leptin signals are adequately relayed.

Researchers have begun to develop treatments to prevent children from carrying extra weight into their adult years. Scientists at the Massachusetts Institute of Technology (MIT), however, have found that anti-obesity drugs that suppress appetite by blocking so-called



Bone density scans provide images of body composition in wild-type (left panel) and leptin-deficient (right panel) mice. Leptin deficiency is associated with increased fatty tissue. (Sebastian Bouret, Ph.D. / University of Southern California)

cannabinoid receptors in the brain could also interfere with children's brain wiring during development.[7] Synthesized in the brain, cannabinoids are structurally related to tetrahydrocannabinol, the active ingredient in marijuana and a known appetite stimulant.

The anti-obesity drugs include rimonabant, marketed by Sanofi-Aventis under the trade name Acomplia, which has been approved for weight loss in Europe and awaits approval by the Food and Drug Administration (FDA) for use in the United States.

The MIT scientists used a well-known experiment to examine brain plasticity (its ability to change based on experience); they temporarily covered one eye in mice soon after they were born, inducing a loss of synapses in the covered eye. Even one day of vision loss caused the synapses to shift to the uncovered eye. Injecting the mice with a cannabinoid receptor blocker stopped the synapses from shifting, suggesting that the cannabinoids play a key role in the early stages of synapse development. Blocking cannabinoids, as anti-obesity drugs such as Acomplia do, could hinder this development process, the researchers say, suppressing the brain wiring necessary for normal development in children.

Researchers caution, however, that psychiatric problems, including severe depression and suicidal thoughts, may be a greater potential problem linked to cannabinoid antagonists than childhood brain development. In 2007, a panel recommended that the FDA not approve rimonabant for use in the United States because of this increased risk.

Approved treatments have limitations, as well. While many people on weight-loss plans successfully shed pounds, others, especially those who typically overeat, become hungry when dieting and increase their food intake even as they attempt to lose weight. Researchers at the Columbia University Medical Center/New York Presbyterian Medical Center reported in the *Journal of Clinical Investigation* that low levels of the hormone leptin cause changes in food intake and energy expenditure that lead to weight gain during dieting.[8] Using visual food cues, the scientists showed that leptin-mediated changes in areas of the brain that regulate the emotional and cognitive aspects of eating led to overeating after weight loss. The researchers say their findings "support the pivotal role of leptin in body weight regulation as a primary 'defense hormone' against loss of body fat following otherwise successful weight loss."

Other research gives extra incentive for researchers to reduce

the prevalence of obesity. In the Cellular Neurobiology Laboratory at the Salk Institute, David Schubert has shown how obesity, type 2 diabetes, and Alzheimer's disease may be linked.[9] While the research is not directly related to obesity, Schubert's findings show that people with type 2 diabetes, a leading cause of which is excess weight, are nearly 65 percent more likely than those without diabetes to develop Alzheimer's disease.

Schubert's research builds on other studies showing that obesity and Alzheimer's are linked. In a May 2008 paper in *Obesity Reviews*,[10] a team of researchers at the Johns Hopkins Bloomberg School of Public Health examined two decades' worth of research that coupled obesity with an increased risk of Alzheimer's and other forms of dementia. In most of the studies they analyzed, the researchers said obesity increased the risk of Alzheimer's by 80 percent. Preventing or treating obesity at an early age, they said, could "play a major role in reducing the number of dementia patients."

Global Initiatives to Combat Epidemic

As the 2008 research findings show, curbing obesity will require more than simply eating less and exercising more. Scientists continue to further their understanding of the biochemistry of appetite, and drug companies seek new drugs to help rid us of unwanted pounds. In the United States, policymakers push for better food labeling and nutritional information on food packages. An increasing number of schools alter their cafeteria menus to offer a more healthful diet. Many companies offer incentives to employees to lose weight (and thereby reduce the companies' health-care costs).

Countries such as Brazil, Australia, and Singapore have started to address their growing obesity problem; however, it will take time for their strategies to be implemented and for results to become evident. The International Obesity Task Force, part of the International Association for the Study of Obesity, has established a program aimed at the prevention and management of obesity through raised awareness of the problem among governments, health-care professionals, and the community. And the World Health Organization, through its Global Strategy on Diet, Physical Activity, and Health, is helping to create public policies that promote the availability and accessibility of low-fat, high-fiber diets, as well as monitoring the response to the burden of obesity and associated medical conditions through clinical

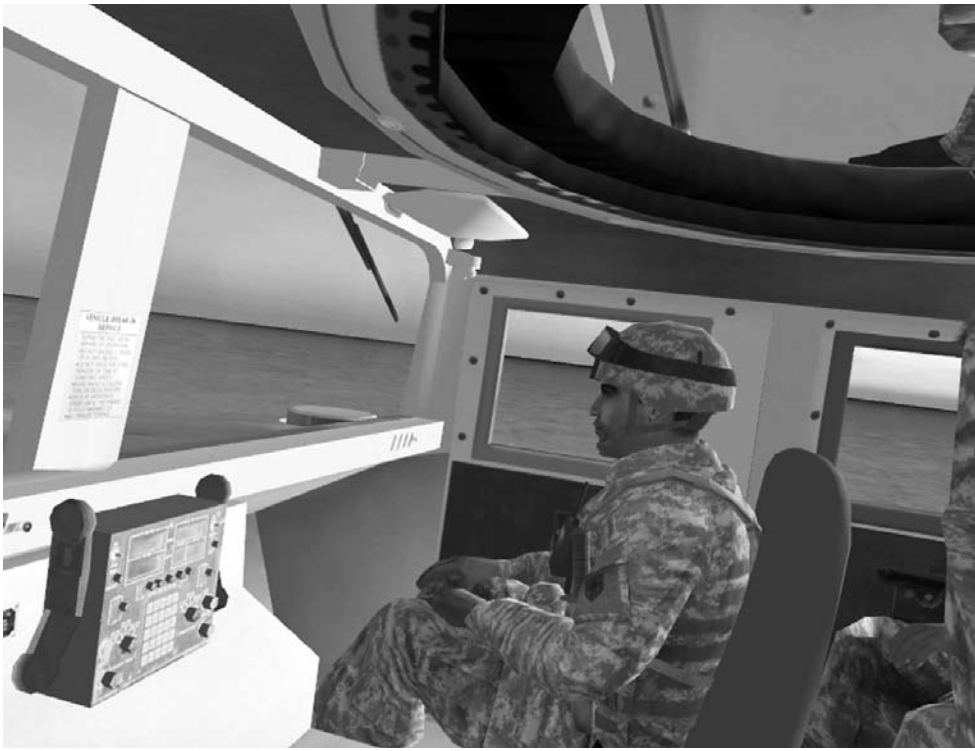
and training programs to ensure effective support of those afflicted with obesity.

They have their work cut out for them: currently there are more than 1 billion overweight people in the world—nearly one-sixth of the population—and 300 million of those overweight people are obese.

POST-TRAUMATIC STRESS DISORDER AND TRAUMATIC BRAIN INJURY

Healing the Battered Brain

Kayt Sukel



A scene from Skip Rizzo's Virtual Iraq application, which allows veterans to revisit traumatic scenes from their service

(Skip Rizzo, Ph.D. / USC Institute for Creative Technologies)

For decades, researchers have hoped to uncover the biological mechanisms behind post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI), increasingly common afflictions among both soldiers and civilians. In 2008, researchers renewed their focus on these conditions and sought to identify the processes that will provide new avenues for prevention and treatment.

The findings include a study that shows that damage to certain areas of the brain may actually protect against the development of PTSD. Coupled with other neuroimaging studies, these results provide a probable neural circuit for the disorder that may yield new discoveries about who may be more susceptible to it as well as new targets for treatment. By targeting fear extinction at the neural level, two new compounds are showing promise in both the prevention and treatment of PTSD. And finally, scientists have discovered that progesterone is no mere sex hormone. Preliminary studies suggest that the sex steroid may help protect the brain from the "cytotoxic cascade" of TBI.

Post-traumatic Stress Disorder

Researchers investigating the neural mechanisms of PTSD want to understand why one soldier develops the disorder while the soldier's immediate comrades do not and why certain treatments may work for one individual but not another.

Steve Centore was the leader of a Department of Energy Hazardous Materials Response Team when he first set foot in Ground Zero after the September 11, 2001, attacks. He was testing for potential contaminants in the debris or air that might be dangerous to people working within the perimeter. While running test protocols, Centore and his team were in plain sight of the "bucket brigades," rescue workers moving debris away in five-gallon buckets in hopes of discovering survivors. "We would walk around the pile and do our tests," he said. "While you were doing them, you'd look down. And what you thought was a rubber hose, just something peculiar that caught your eye, would instead be a severed arm."

Centore said that you couldn't help but see these gruesome artifacts while working at Ground Zero. Years later, he still sees them. In 2005, after suffering from flashbacks and panic attacks so severe that he became afraid to leave his home, Centore was diagnosed with PTSD. The disorder, often referred to in the past as "shell shock" or "battle

fatigue," has dramatically changed his life, rendering him unable to work, afraid to sleep, and reluctant to venture out of his house.

According to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*), the standard handbook for mental health professionals, PTSD is the development of characteristic symptoms after experiencing an extreme traumatic event that threatens death or bodily harm. Those symptoms include reexperiencing the event over time (i.e., flashbacks), persistent avoidance of stimuli that remind individuals of the event, hypervigilance, difficulty controlling emotions, sleep disturbances, and social avoidance behaviors. The disorder can be debilitating, wreaking havoc with work and social lives.

PTSD is not a new phenomenon. Greek historian Herodotus made mention of battle-related stress symptoms after the Battle of Marathon in 490 B.C. But until the Vietnam War, many viewed "shell shock" more as a sign of cowardice than as a true psychological disorder. Soldiers from conflicts such as the Civil War and World Wars I and II were often stigmatized for "battle fatigue" and, when compassionately diagnosed, treated with bed rest, isolation, or early versions of talk therapy. The Vietnam War was a turning point. With the influx of returning veterans, many of whom had difficulty adjusting to the civilian world, "shell shock" gained new respect as a true psychological disorder (as did its new moniker, PTSD). Since health professionals did not understand the underlying neuropathology of the disorder, they most often treated patients with counseling, exposure therapy, and anti-anxiety medications.

Looking to the Past to See the Future

In a novel approach to studying PTSD and the brain, Judith Pizarro Andersen and colleagues at the University of California, Irvine, looked to old paper medical records instead of genetic studies or neuroimaging protocols. Mining Civil War files, the researchers were able to extrapolate the long-term health effects of traumatic war experiences on thousands of Civil War vets. Their research, published in the February 2006 *Archives of General Psychiatry*, revealed that being a prisoner of war, being wounded, or witnessing the deaths of a large number of fellow soldiers was linked to higher incidence of cardiac, gastrointestinal, and nervous disease later in life.[1]

Andersen said that the most surprising finding was that veterans who entered service when they were younger than twenty were


Roxane Cohen Silver (left), Judith Pizarro Andersen (right) and colleagues gathered and analyzed information on the effects of traumatic war experiences on Civil War soldiers. (Roxane Cohen Silver, Ph.D., Judith Andersen, Ph.D. / University of California, Irvine)

more susceptible to later health problems. "That age was a powerful predictor [of] whether the soldiers would get chronic diseases earlier in life," she said. "And it also influenced if they would die earlier—their actual survival."

In the same issue of the journal, Roger Pitman commented in his own review that pathways that process fear and fear extinction—an inhibitory learning process that allows a fearful memory to lose its potency over time—may not have fully matured until the age of twenty.[2] "We need to really think about what age means in a neurological way," said Andersen. "The idea that some of those neurobiological pathways aren't developed yet to handle these events makes sense. But it needs to be better understood."

Brain Differences in PTSD

Although PTSD has been classified as a psychiatric illness for nearly a century, only in recent years has research given us greater understanding of the neurobiological basis of the disorder. Lisa Shin, a researcher at Tufts University, has been studying brain activation differences in PTSD patients for more than a decade. Her work, using positron-emission tomography and functional magnetic resonance imaging (fMRI), has found significant differences in brain areas linked to memory and emotion in patients with PTSD.[3]

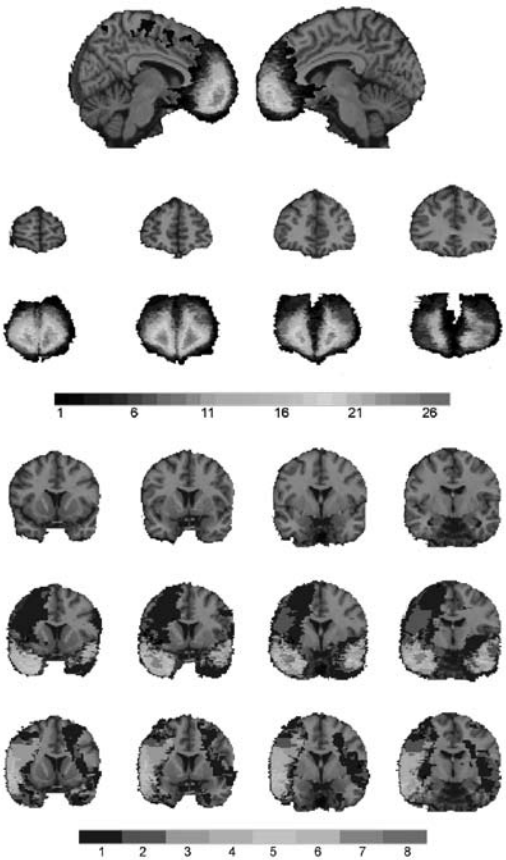
The amygdala, part of the limbic system and implicated in both memory and fear processing, is one such area. "In PTSD, the amygdala is hyper-activated," said Shin. "When you scan people as they remember traumatic events or look at fearful faces, the amygdala is responsive to that. And many studies with PTSD patients have found exaggerated responsivity to those kinds of stimuli."

Just as important, the medial prefrontal cortex (PFC) is underresponsive to fearful stimuli, Shin said. "Perhaps the medial prefrontal cortex can't inhibit the amygdala. It's a nice circuit to look at,

considering that it is the same circuit involved with fear conditioning and extinction." Shin's lab is currently looking at brain activation patterns as a way of predicting response to treatment.

Research by Jordan Grafman, a senior investigator at the National Institute of Neurological Disorders and Stroke, and colleagues suggests that focal brain damage in the amygdala and the ventromedial PFC may actually protect the brain from PTSD. In a study published in the February 2008 issue of *Nature Neuroscience*, Grafman and his collaborators looked at Vietnam veterans who had both brain injury and exposure to war trauma.[4]

"When people have a brain injury, you generally don't expect it to be helpful," said Grafman. "But in this case, when the injury was in the amygdala or ventromedial prefrontal cortex, it did protect against the constellation of impairments that result in PTSD." The finding implies that these areas play a key role in the development of PTSD and offers future researchers a good place to focus, Grafman argues.



A study examined Vietnam veterans who both sustained brain damage and experienced war trauma. The subjects were grouped according to the site of the injury, into the ventromedial prefrontal cortex group (top) or the amygdala and temporal lobe comparison group (bottom). In the images, the shade of the brain area corresponds to a scale at bottom indicating the number of veterans who exhibited brain damage there. (Jordan Grafman, Ph.D. / National Institute of Neurological Disorders and Stroke)

The thalamus is also of interest in PTSD. Keith Young, a researcher at the Center of Excellence for Research on Returning War Veterans, part of the Central Texas Veterans Healthcare System in Waco, focuses on alterations in brain anatomy that may predispose individuals to stress disorders.

"Many studies focus on the frontal cortex, where fear memories are formed and then go on to influence emotion," said Young. "The thalamus is an input to these areas. Both vision and hearing go through the thalamus before getting repackaged, so to speak, and sent to the frontal cortex and limbic system."

In a paper published in the June 2008 *British Journal of Psychiatry*, Young and colleagues link a certain genotype in humans—one that underlies serotonin transport function—to the development of PTSD. This particular genotype results in an increased number of neurons in the thalamus. And that, in turn, can make those individuals more susceptible to the development of major depression and PTSD.[5] Young hypothesizes that this enlarged thalamus may amplify fearful memories, making people more susceptible to these disorders. "When people have this enlarged thalamus, they are able to shift more of the sensory input to the limbic system," he said. "So these people are basically capable of producing more and stronger fears that can lead to PTSD."

Young believes that this genotype could help doctors identify individuals who are more vulnerable to PTSD before they are exposed to trauma as well as help generate new treatments.

Fear Conditioning and Extinction

Many people live through traumatic situations, but most of them do not develop debilitating psychiatric disorders. Michael Davis, a neurobiologist at Emory University, studies the cellular mechanisms underlying fear extinction. He argues that the symptoms of a disorder such as PTSD, particularly the vivid flashbacks, are a powerful type of fear conditioning that can train the mind to remain anxious even when there is no longer any danger.

"The memories are hard to get out of the mind," Davis said. "The condition can be triggered by signals in the environment that remind people of the trauma. Vietnam veterans may smell Asian food, experience a warm, muggy night, smell sulphur, and that triggers the flashbacks." The flashbacks, in turn, strengthen the body's response.

But many PTSD patients can be successfully treated with techniques that promote extinction of the fearful memory. "If you can remind people with PTSD of the bad things that happen to them and explain that they won't happen again, do that again and again, so that they learn that if they face these fearful things nothing bad will happen, they will eventually get over that fear," said Davis. But despite knowing exquisite detail about how animals learn to fear initially, researchers still have much learn about how to extinguish that fear.[6]

For some individuals with PTSD, fears either are not extinguished or are only temporarily quieted. "It's a big question—why is it that some patients continue to exhibit high fear and anxiety when there is no longer any danger present?" asks Mohammed Milad, a researcher at Massachusetts General Hospital. In a study published in the June 2008 *Journal of Psychiatric Research*, Milad and colleagues examined fourteen pairs of identical twins in which one had PTSD. The researchers assessed extinction learning and found that the retention of the extinction memory was deficient in those with PTSD. Just as important, the nature of the twin studies suggests that the deficit was acquired with the trauma as opposed to being a predisposing factor.[7]

Milad hypothesizes that a faulty ventromedial PFC makes it difficult for individuals to recall prior inhibitive learning. "The idea is that if you have a healthy ventromedial prefrontal cortex, you can convert inhibitive learning to long-term memory. If [the ventromedial PFC] is not healthy, presumably you can learn not to fear in the short term but that fear will come back over time." He is continuing to study pathologies in the PFC that may result in anxiety disorders.

Enhancing Fear Extinction

Davis's past work has demonstrated that the fear circuit in the brain, involving areas such as the amygdala, has to actively work to extinguish fearful memories. Part of that process involves the activation of N-methyl-D-aspartate acid (NMDA) receptors in those areas. Using rat models, they found that a drug called D-cycloserine facilitates NMDA receptor function, in turn promoting fear extinction. Davis and colleagues are now testing the use of D-cycloserine in humans.

"The drug sticks to receptors in the amygdala neurons, changing their shape," Davis said. "This change seems to help lay down that inhibitory memory we call extinction." But he asserts that much

about how the extinction process is initiated and carried out remains a mystery.[8]

Propranolol, another drug that may help promote fear extinction, has historically been used to treat hypertension and migraine headaches. Karim Nader and collaborators at McGill University found that the drug helped to stop the reconsolidation of fear memories in humans. When an individual learns something, he must consolidate the memory in the brain in order to access it later. But over time, some memories may grow unstable and need to be reconsolidated.

"Reconsolidation is a new process that uses some of the same mechanisms as consolidation," Nader said. "And with fear memories, even very old ones, you can essentially get rid of them by blocking this reconsolidation process."

In a study published in the May 2008 *Journal of Psychiatric Research*, Nader's group gave PTSD patients propranolol and then asked them to recount their traumatic memory.[9] "The idea is that if you ask people to remember that traumatic memory then maybe it goes back to a more unstable state," said Nader. "That gives us a window to use propranolol to reduce the strength of the memory."

When speaking of the traumatic events, study participants who received the drug showed a lower fear response as gauged by metrics such as heart rate and the skin's electrical resistance. The researchers hypothesize that propranolol somehow interferes with the emotional reconsolidation of the memories as the situational details remain intact. "If you give them propranolol, they remember the information, but they just don't get the same emotional boost from the event that they got before," said Nader.

Reliving Traumatic Memories

Past clinical and neuropsychological studies have indicated that the path to extinction involves confronting traumatic memories head-on. But is it enough just to recall a memory? Could extinction perhaps happen faster or last longer if a person with PTSD could somehow relive the past trauma in a more tangible manner?

Skip Rizzo, codirector of the Laboratory for Virtual Reality, Psychology, Rehabilitation, and Social Neuroscience at the University of Southern California's Institute for Creative Technologies, helps develop virtual reality (VR) applications that help clinicians reimmerse patients into a past trauma.

Skip Rizzo's virtual Iraq application allows patients to confront their memories of traumatic events, such as an attack on a convoy. (Skip Rizzo, Ph.D. / USC Institute for Creative Technologies)

"Over the last twenty to twenty-five years, we've found that exposure therapy is one of the most effective to treat PTSD. But we don't know what's going on in the hidden world of imagination," said Rizzo. "VR is a tool that can deliver that exposure therapy in a more controlled environment. Patients are immersed in a virtual world that can systematically deliver elements that they may be fearful of."

Rizzo's group has designed applications for fear of flying and fear of heights. But the researchers have received recent attention for their virtual Iraq system, which allows Operation Iraqi Freedom veterans with PTSD to virtually return to the scene of the emotional trauma.[10]

"A patient's worst event may be a convoy being blown up with an improvised explosive device," said Rizzo. "With the VR system, a therapist might start off having the patient just sit in a Humvee, look around a little. Once he gets comfortable with that, the therapist can add a little more at a time, gradually approaching those elements that the patient recalled as the seminal event."

Rizzo said that a virtual environment allows the patient to process the fearful memories, eventually habituating to them. And at one therapy site, Rizzo reports that eighteen individuals progressed enough after three months of therapy to no longer meet the case definition for PTSD. Rizzo plans to look more closely at what is happening in the brain during VR therapy in future work.

Hormone Treats Traumatic Brain Injury

Another artifact of war is an increase in blunt head traumas and traumatic brain imjury (TBI). The effects of TBI range from mild to

severe, but in all cases a blow to the head causes damage to the brain. That damage can trigger problems that extend injury beyond the area of impact.

"The injury sets off what is called a cytotoxic cascade of events," said David W. Wright, a researcher at Emory University's Emergency Medicine Research Center. At the point of injury, neurons may die off simply from the trauma. And as those neurons die, they release chemicals that are toxic to surrounding cells, perpetuating through the network. The body's natural response to this is edema, or swelling, which in the enclosed skull can result in further cell death.

"These cascades can continue for days, weeks, even up to years," said Wright. "It's a cyclic path to more cell death across the brain." And the results can be severe. Patients with a mild form of injury may have symptoms such as slurred speech, loss of coordination, and weakness in the extremities. Those with more severe injuries can suffer from permanent neurological impairment. Patients with TBI-related injury caused by the improvised explosive devices (IEDs) common to the Iraq conflict may have even more formidable damage to the brain. In 2008, the U.S. Department of Veterans Affairs proposed that blast-related TBIs be considered a special neurological condition.

"With an IED, you get a shock wave that is transmitted through the abdomen up to the brain, compressing the blood," said Joseph Coyle, a researcher at Harvard Medical School. "This causes damage in the deep brain structures as well as shearing that damages the neuronal connections in the brain." Some hypothesize that the damage to these primitive brain structures may result in a higher susceptibility to PTSD as well as a slower appearance of neurological symptoms.[11] However, a thorough study of these hypotheses has yet to be conducted.

For decades, researchers believed that nothing could be done to alleviate the brain damage that follows TBI. Wright has initial results that suggest that progesterone, commonly thought of as a "female" hormone, may limit these cytotoxic effects, reducing the amount of damage when artificially introduced immediately after a blunt head injury. In a study published in the February 2008 issue of *Brain Injury*, Wright and colleagues showed that application of progesterone reduced cerebral swelling and helped rats with a model of traumatic brain injury recover.[12]

Wright has also successfully used progesterone with human patients. A small pilot study of one hundred patients resulted in a 50

percent reduction in mortality compared with a control group that received a placebo, as well as improved neurological function after thirty days in patients with moderate TBI.[13] His research group will soon start a four-year study of more than 1,000 patients at seventeen trauma centers nationwide.

Wright's work addresses a method of minimizing injury. Gary Strangman, another researcher at Massachusetts General Hospital, is using fMRI scans to try to predict which TBI patients will respond to a language rehabilitation protocol after the damage has been done.

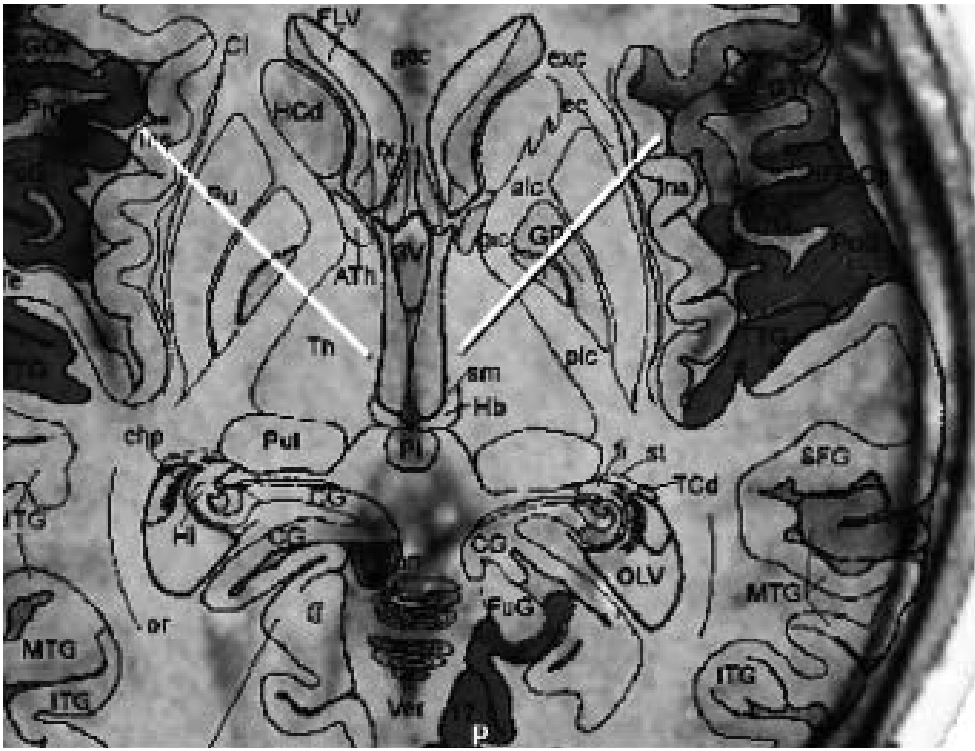
Though two patients may both be classified as mild cases, the injuries both occur and manifest themselves in different ways with different symptoms. But even with that kind of dissimilar damage among participants, Strangman and colleagues found that patterns of activity in the left lateral PFC could help predict how well patients responded to a semantics-based list-learning strategy, a method of remembering a list of words after grouping them into meaningful categories that would help cue recall. The results were published in the May 2008 issue of the *Archives of Physical Medicine and Rehabilitation*.[14]

"Our purpose was to see whether we could use fMRI information to predict outcomes," Strangman said. "This kind of strategy could help us better tailor rehabilitation strategies to individuals in, say, five to ten years."

Strangman's group plans to do further studies to see if fMRI activation in the brain can help predict response to other rehabilitation strategies.

ROUNDUP
More Important Findings in 2008

John Timmer



Map of a brain that has received deep brain stimulation surgery, with darkened areas indicating affected regions and white lines indicating device location
(Marco Sassi, M.D. / Istituto Galeazzi)

The preceding chapters presented in-depth examinations of six areas of brain research that saw important returns in 2008. However, this year's promising advancements and discoveries ranged over many other areas of brain science as well. In particular, current research on obsessive-compulsive disorder, pain, autism, fragile X syndrome, sleep, deep brain stimulation, and neuroethics merit brief mention.

Understanding Fear Could Help Treat Obsessive-Compulsive Disorder

People suffering from obsessive-compulsive disorder (OCD) have traditionally had two choices: behavioral therapy for the condition or drugs for the symptoms. Now they may have a third option, in the form of a drug that improves the effectiveness of behavioral therapy.

Behaviors that resemble OCD were described as far back as the 1600s, and the first clinical description of the condition appeared in a French psychiatry text that was published in 1837. People who suffer from OCD frequently experience the recurrence of unwelcome thoughts and repetitive or ritualized behaviors; these generally appear late in childhood. Some experience anxiety or fear that lapses in these behaviors might cause something bad to happen.

OCD affects approximately 2.2 million American adults. Those with OCD also appear to be prone to other anxiety disorders and depression. Like patients with depression, people with OCD can be treated with selective serotonin reuptake inhibitors (SSRIs). Variations in the gene for the serotonin transporter have been shown to be associated with an increased risk of developing OCD.

Research in animals has found that they can learn to overcome

Sabine Wilhelm (right) pantomimes an exposure-based behavioral therapy session with an assistant who is pretending to be a patient with a fear of knives. Similar therapy sessions have shown to be effective in reducing the anxiety associated with OCD. (Sabine Wilhelm, Ph.D. / Massachusetts General Hospital)

fear through a process that involves neurons with receptors for the chemical N-methyl-D-aspartate (NMDA). These findings have suggested that enhanced NMDA signaling may hasten the process of learning to overcome fear and anxiety.

A team of researchers at several New England hospitals decided to test whether our knowledge of animal behavior could be used to improve treatments of human anxiety. The results of their work were published in March 2008 by the *American Journal of Psychiatry*.[1] The researchers recruited patients with OCD and enrolled them in a program of biweekly behavioral therapy sessions. This counseling technique can help patients learn to reduce the anxiety associated with OCD, but its success rate has been low. Half of the patients in the study received a placebo, while the other half received a drug, cycloserine, that increases NMDA receptor activity. Although both populations showed improvement, those who received cycloserine had a larger reduction in OCD symptoms, a difference that persisted for at least a month following treatment. Better still, those receiving the drug saw an improvement in symptoms of depression that often accompany OCD.

This study joins earlier work that described benefits of a combination of cycloserine and therapy in the treatment of other anxiety disorders, including social anxiety and the fear of heights. The researchers call for larger trials of the procedure that will provide a clearer picture of how significant the benefits are. Pursuing these trials should be made easier by the fact that cycloserine was approved for human use more than twenty years ago, as a treatment for tuberculosis.

Zeroing In on Pain with Targeted Drugs

Treatment of pain presents many distinct challenges. Most drugs marketed for limiting the sensation of pain have a number of drawbacks, including addictive properties, reduced effectiveness over time, and side effects. Now the increased understanding of nervous system function is allowing scientists to design drugs targeted to specific types of pain.

Ion channels are the floodgates that regulate the flow of molecules in and out of the body's cells. Types of ion channels belonging to the transient receptor potential (TRP) family are essential for the sensation of pain. Different members of this family specialize in responding to different types of stimuli, such as cold, heat, and physical strain.

Existing chemicals that block pain, from the capsaicin found in chile peppers to the itch-relief drug lidocaine, all work by targeting either TRP proteins or sodium channels.

Migraines can cause debilitating pain, and some sufferers respond poorly to existing painkillers. During the past decade, research has linked migraines to increased blood flow in the brain, a process that is under the control of the nervous system. Nerves in the head produce a protein, calcitonin gene-related peptide (CGRP), that causes blood vessels to dilate, increasing blood flow. Accordingly, drugs that block CGRP function should alleviate migraine symptoms.

The first such drug may be getting close to market. At the 2008 meeting of the American Headache Society, clinicians presented the results of a Phase III clinical trial of the CGRP antagonist MK-0974. This type of drug blocks the binding of CGRP to receptors in order to inhibit blood vessel dilation.[2] The drug treated migraine symptoms as effectively as existing therapies, but it produced significantly fewer side effects.

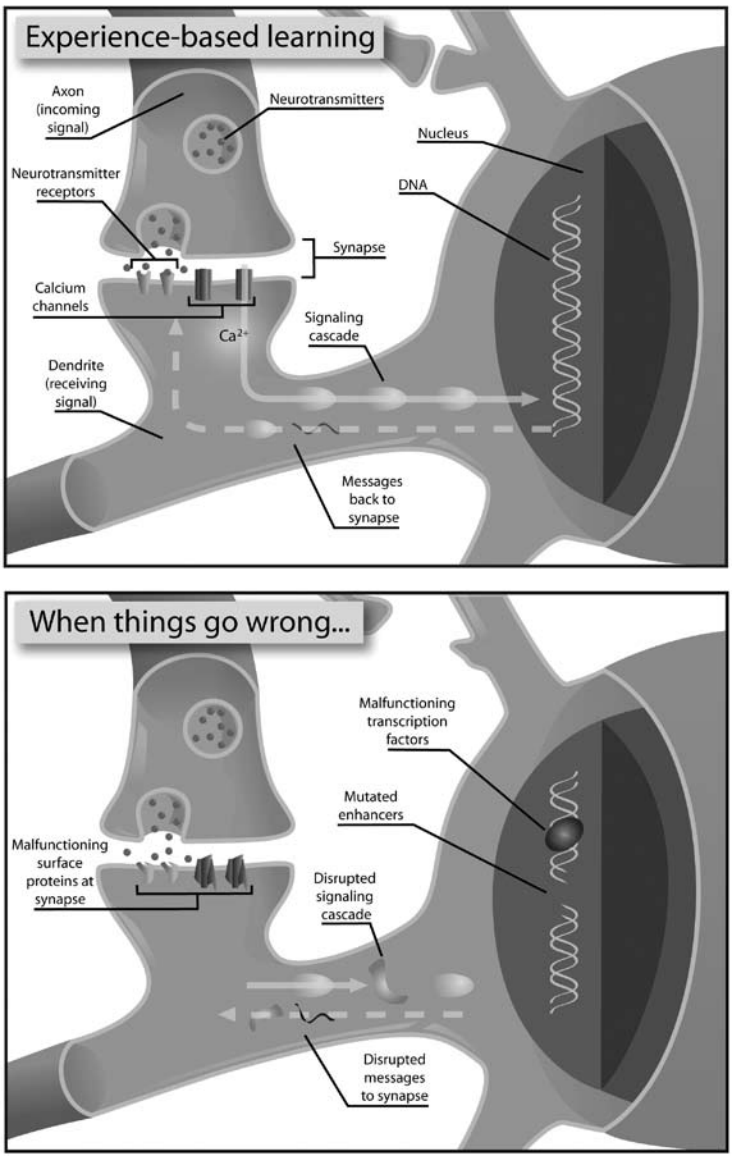
Researchers are also making progress in finding new methods of treating pain from injury and inflammation. They have identified mutations in a specific sodium channel, NaV1.7, that alter people's perception of pain. Loss of the NaV1.7 channel causes indifference to pain, indicating that it is a potential target for painkillers.

Researchers from Merck have determined that a protein in tarantula venom specifically binds NaV1.7 and blocks its function, and they have identified a part of the channel that is essential for this binding.[3] Although the tarantula protein is not appropriate for use as a drug, its interaction with NaV1.7 will act as a model for designing targeted pain therapies.

Autism Genetics Reveals Many Causes

The social withdrawal displayed by autistic children was once thought to be the product of poor parenting skills. However, as the incidence of the disorder has risen alongside an increase in scientific research and public awareness, it has become increasingly clear that autism has an underlying biological basis. Evidence now suggests that even sporadic (nonhereditary) cases of autism have a genetic component, and that the diagnosis may encompass a number of distinct underlying disorders. Two studies highlight our new understanding of the origin of these autism spectrum disorders (ASDs).

A neuro-genetic model of autism



Gene mutations can lead to a variety of cellular mishaps that compromise the brain's ability to form relevant connections in response to experience, leading to autism. The top image shows how experience-based learning occurs in the brain, with an electrical signal traveling down the neuron's axon, reaching the synapse, releasing chemical messengers known as neurotransmitters that cause special channels to open on the receiving neuron. A cascade of signals then travels to its nucleus, launching a program involving multiple genes that communicates back to the surface, enabling the neuron to strengthen, weaken, create, or destroy synapses or make a different kind of synapse. Some cellular mishaps are described in the bottom image. (Graham Paterson / Children's Hospital Boston)

Studies in twins indicate that genetics play a dominant role as a cause of autism. A 2007 study found that in sporadic cases of autism there is a high frequency of a genetic abnormality called copy number variations (CNVs). CNVs occur when a large segment of the chromosome is either missing or duplicated; they occur quite frequently in humans, often with no symptoms. A 2008 study in the *New England Journal of Medicine*, performed by the Autism Consortium, found that CNVs are associated with inherited forms of autism as well.[4]

The team identified a specific area of human chromosome 16 (16p11.2) that was frequently altered in patients with ASDs. In some cases, the area and the genes it contains were simply absent, but other patients actually had extra copies of 16p11.2. The results suggest that the number of copies of the gene(s) in the area may play a greater role in these cases of autism than the mere presence or absence of that part of the chromosome.

Separately, an international team of researchers studied a panel of families that included autistic children that are the product of marriages between cousins, reasoning that these individuals were likely to carry two copies of an identical region of DNA.[5] The study identified six new genes associated with autism and also identified additional areas of the human genome that are deleted in those with autism. One gene, NHE9, was identified in patients with both ASD and epilepsy; the authors found that NHE9 was also damaged in unrelated individuals with autism-like symptoms.

The identified genes perform a variety of functions, including enabling nerve cells to transmit signals and regulating the location and stability of proteins within the nervous system. The diverse gene functions, and the frequent co-occurrence of ASD with other nervous system disorders, led the authors to conclude that autistic symptoms are caused by a variety of underlying disorders. "The genetic architecture of autism resembles that of mental retardation and epilepsy," they write, "with many syndromes, each individually rare."

Fragile X Theory Points the Way Toward Potential Therapies

Experiments using a mouse model of fragile X syndrome have provided support for a theory regarding the causes of this human genetic disease and point the way toward potential drug interventions.

Fragile X syndrome is one of the most common inherited forms of mental retardation and results in additional symptoms that include autism spectrum disorder, seizures, and several physical abnormalities. This disorder was first linked to the X chromosome in 1943. In 1969 researchers associated it with a change in the structure of the affected X chromosome. In 1991 scientists identified the molecular basis for this change as the product of a mutation in which a small, repetitive segment of DNA is amplified, resulting in many tandem copies of the repeated sequence. As the number of repeats increases, the production of the protein encoded by the fragile X gene, FMRP, decreases.

FMRP controls the production of many proteins in nerve cells, but evidence has suggested that a key target of FMRP is a receptor for the neurotransmitter glutamate called mGluR5; when FMRP is absent, as in fragile X patients, signaling through mGluR5 is overactive. In a paper published in the final weeks of 2007, researchers tested this directly by genetically reducing mGluR5 in mice.[6]

Mice with mutations that eliminate the FMRP gene displayed characteristics similar to some of those seen in fragile X patients. When those same mice were missing one of the two copies of the mGluR5 gene, however, the majority of the defects were suppressed. The researchers found that protein expression in nerve cells was restored to normal levels in these mice, and this corresponded with a return to a normal cell structure. Tests of behavior and memory also showed that the reduction of mGluR5 restored the mice to normal. Even changes in body size caused by the loss of FMRP were suppressed by the reduced presence of mGluR5.

Many drugs exist that reduce the activity of mGluR5 receptors, and other such "antagonists" are now under development, although none is approved for therapeutic use in treating fragile X syndrome in humans.

In 2008, Mark Bear, who led the research published in late 2007, and colleagues published a review of fragile X in which they supported the "increasingly strong case" for human clinical trials with mGluR5 antagonists.[7] On the strength of this and other animal research, a few small human studies commenced in 2008, for fragile X syndrome and other disorders.[8]

Building a Unified Theory of Sleep

The function of sleep in humans remains a matter of debate, as does its very existence in other animals. Two reviews in 2008 addressed the sleep cycle across species, and a 2007 study proposed a model of human sleep controlled largely by basic metabolism needs.

On the molecular level, many of the proteins that control the circadian cycle of waking activity and sleep are conserved from flies to humans. However, a 2008 review by Jerome Siegel argued against the widely accepted platitude that "all animals sleep." Siegel found the notion unverifiable using existing research.[9] Only 50 of nearly 16,000 vertebrate species have been tested for the commonly held criteria for sleep.

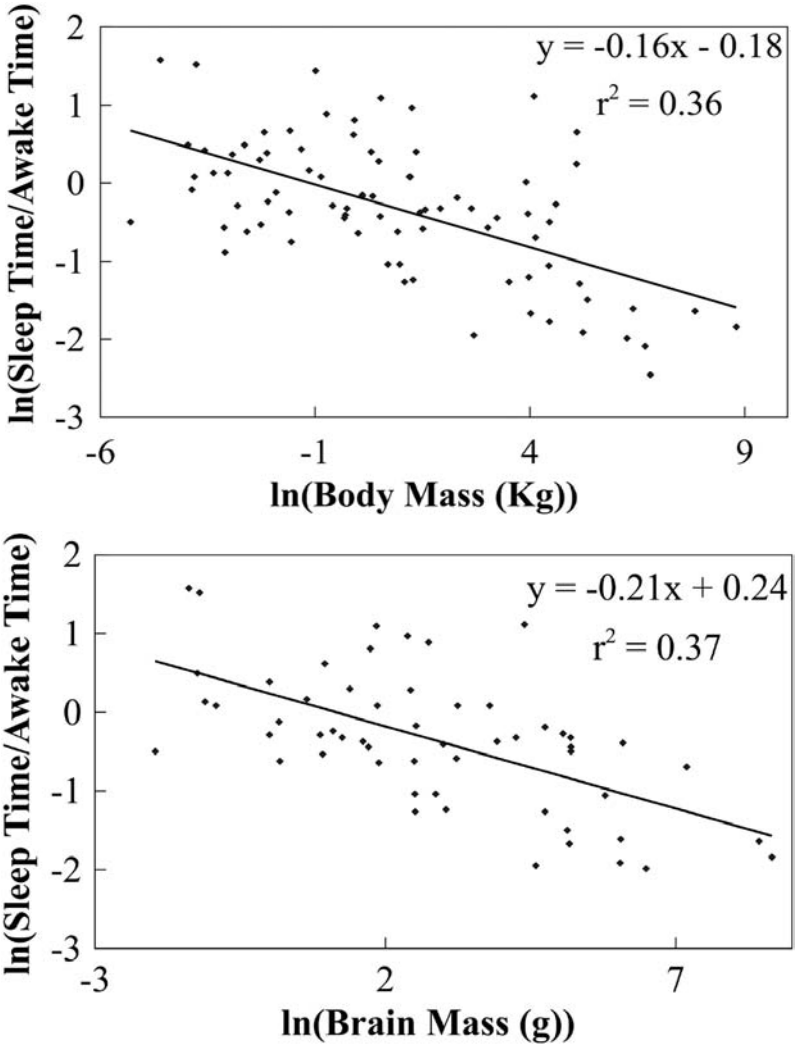
Indeed, the activity we think of as sleeping appears to vary wildly from species to species. Another 2008 review by Siegel and Ravi Allada looked at the brain patterns of various animals sleeping.[10] Sleep studies in terrestrial mammals (including humans) typically measure electrical activity in the brain with an electroencephalogram (EEG). Siegel and Allada's review found an absence of identifiable EEG sleep traits in a diverse set of animals, which suggests that these patterns may not represent an essential feature of sleep for all animals.

Some sleep activities may be unique to certain species. For those molecular aspects of sleep that do seem common from flies to worms to humans, studying insect genetic models may help uncover the basis of sleep in more complex organisms, such as humans.

Other recent research has focused on two potential functions for sleep. The first is its use in fostering the consolidation of learning and memories derived from the waking hours. The second emphasizes its role in allowing the brain to repair the damage caused by its unique metabolic requirements.[11]

Each of these proposals has experimental support. A role for metabolism is suggested by the fact that smaller animals, which tend to have much higher overall body metabolisms, sleep for significantly longer than larger ones; for example, mice typically sleep for more than half the day, while elephants sleep for as few as four hours daily. Research published in March 2007 by Van Savage and colleagues at the Santa Fe Institute suggests that cell volume and metabolic rate vary depending on the animal's size, supporting the notion that sleep may be a response to the metabolic needs of the body's cells.[12]

In favor of memory consolidation, electrode-based recordings



The top graph, a logarithmic plot of several species' body mass and sleep times, shows that the ratio of time spent asleep to time spent awake declines as body mass increases. The bottom graph shows that ratio similarly decreasing as brain mass increases. (Van M. Savage, Ph.D. and Geoffrey B. West, Ph.D.)

of the brains of sleeping rats have revealed patterns of activity that recapitulate ones observed during their waking activity.

Side by side, these two proposals appear to be inconsistent. If large animals spend most of their day awake, then their complex brains should require more time to consolidate memories. Also, the ratio of brain to body size varies dramatically across species, which means that for different animals the brain may be responsible for different percentages of the overall body.

The theory published by Savage relates body mass and metabolism to both time spent asleep and the proportion of time spent in REM sleep, a normal stage of sleep that appears important to memory and other waking functions. The researchers' model accurately predicts both of these aspects, using as input the weight and metabolic rates of ninety-six species of mammals that differ in body size by as much as a factor of a million.

The authors conclude that "sleep is a special state of the brain that is devoted primarily to the critical activities of repair and reorganization." At the moment, their theory cannot distinguish between the relative importance of these activities, but they suggest that future biological studies based on their model might provide insight.

Deep Brain Stimulation Therapy Matures with New Targets

In deep brain stimulation (DBS) electrodes implanted in the brain deliver electrical pulses to patients suffering from movement disorders such as Parkinson's disease (PD). The technique has proved highly effective, so much so that the procedure is covered by Medicare. "Whether deep brain stimulation can dramatically help patients with Parkinson's disease and other movement disorders is no longer questioned," wrote Jerrold Vitek of the Cleveland Clinic in a recent review of the field.[13] The frontiers of DBS have now moved on to other maladies, such as clinical depression and Tourette's syndrome.

Vitek notes that the means by which DBS leads to long-term changes in brain activity are not well understood. Nevertheless, the ability to inhibit neural activity suggests that DBS may be an effective treatment for other disorders in which a specific region of the brain has been implicated as being aberrantly active.

Pilot studies are beginning to apply DBS to cases of depression in which other, more traditional forms of therapy have failed. In a 2008 study involving twenty severely depressed patients, 35 percent had a reduction of symptoms a month after DBS was started. By six months after surgery, more than half of the patients had responded to treatment, with seven showing a complete remission of their depression.[14]

DBS has also been used as an experimental therapy for a small number of patients with Tourette's syndrome, a neuropsychiatric disorder characterized by motor and vocal tics. The pathology of

Tourette's syndrome—which in severe cases can cause debilitating obsessive-compulsive and self-injurious behaviors—is still debated, but since 1999 DBS has been applied successfully in multiple brain areas in patients who did not respond to other forms of therapy.

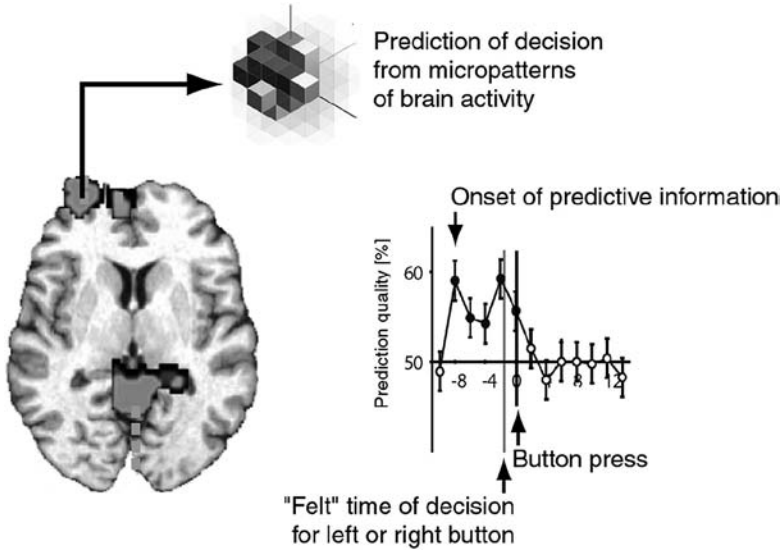
A 2008 study of eighteen patients with severe Tourette's found that several months after the surgery, every patient's symptoms had decreased, with no adverse side effects. This study targeted a specific region in the brain's thalamus, known as the centromedian-parafascicular and ventralis oralis complex, and researchers recommended the procedure as "a useful and safe treatment for severe" Tourette's.[15] However, not all patients responded equally well, and future research will need to investigate the factors that might make a person more or less responsive to the therapy.

Neuroethics: Exploring Expectations of Future Medical Technology

Scientists concerned with neuroethics seek, among other things, to gauge the moral and legal ramifications of current neuroscience research in terms of possible future developments and applications, especially regarding fears and uncertainties of the public. Recently, the use of functional magnetic resonance imaging (fMRI) as lie detector, political compass, emotion monitor, and all-around mind reader has captured much media attention, incensing some scientists who worry about misapplication of the technology but signifying to others promising new areas of research. In particular, research in 2008 raised questions about whether fMRI might predict a person's decisive action before the conscious decision to act is even made.

Functional MRI uses MRI equipment to non-invasively monitor changes in blood flow within the brain, which provides a measure of neural activity. Neural researchers have used it to identify brain areas involved in normal mental processes, and they have used differences in fMRI signals to identify those with mental disorders.

In 2008, John-Dylan Haynes and colleagues at the Max Planck Institute for Human Cognitive and Brain Sciences measured the brain activity of subjects as they were asked to press a button with their left or right hand. The subjects were free to choose a hand at any time, but were instructed to remember the exact moment when they were conscious of making the decision. By identifying the relevant traces



Activity in certain brain regions (shown as dark gray spots) can predict the outcome of a participant's decision up to seven seconds before it is consciously made. At top, a three-dimensional structure depicts a computer-analyzed pattern of activity from one informative brain region. The graph features information from computer-based pattern classifiers that have been trained to recognize predictive activity. (John-Dylan Haynes, Ph.D.)

of brain activity and using a computer to recognize those signals in subsequent subjects, the researchers were able to accurately predict which hand a subject would use to press the button seven seconds before the subject recorded making the decision. In some cases, brain activity (particularly in the frontal and parietal lobes) predicted the move a full ten seconds ahead of the conscious thought.[16]

Common sense suggests that people choose between possible actions by their own conscious volition, but Haynes's study appears to suggest otherwise. The authors write that the delay between the telltale neural activity and the reported choice "presumably reflects the operation of a network of high-level control areas that begin to prepare an upcoming decision long before it enters awareness."

The length of the delay suggests that the results cannot be explained away as a miscalculation on the part of the subject as to when he made the decision, a criticism levied at earlier work in this field. The authors refrain from discussing the moral ramifications of their findings; neither do they mention the potential for clinical or commercial applications.

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THE DANA ALLIANCE FOR BRAIN INITIATIVES

Mission Statement, Goals, and Membership

The Dana Alliance for Brain Initiatives

Imagine a world…

- in which Alzheimer's, Parkinson's, Lou Gehrig's (ALS) diseases, and retinitis pigmentosa and other causes of blindness are commonly detected in their early stages, and are swiftly treated by medications that stop deterioration before significant damage occurs.
- in which spinal cord injury doesn't mean a lifetime of paralysis because the nervous system can be programmed to re-wire neural circuits and re-establish muscle movement.
- in which drug addiction and alcoholism no longer hold people's lives hostage because easily available treatments can interrupt the changes in neural pathways that cause withdrawal from, and drive the craving for, addictive substances.
- in which the genetic pathways and environmental triggers that predispose people to mental illness are understood so that accurate diagnostic tests and targeted therapies—including medications, counseling, and preventive interventions—are widely available and fully employed.
- in which new knowledge about brain development is used to enhance the benefits of the crucial early learning years and combat diseases associated with aging.
- in which people's daily lives are not compromised by attacks of depression or anxiety because better medications are being developed to treat these conditions.

Although such a vision may seem unrealistic and utopian, we are at an extraordinarily exciting time in the history of neuroscience. The advances in research during the past decade have taken us further than we had imagined. We have expanded our understanding of the basic mechanisms of how the brain works, and are at a point where we can harness the healing potential of that knowledge.

We have already begun to devise strategies, new technologies, and treatments to combat a range of neurological diseases and disorders. By setting therapeutic goals, and applying what we know, we will develop effective treatments—and, in some instances, cures.

For all that has been learned in neuroscience recently, we are learning how much we do not know. That creates the urgency to continue basic research that looks at the broader questions of how living things work. This will help to formulate the complex questions that lead to scientific discovery.

The coordinated work of thousands of basic and clinical scientists in multiple disciplines, ranging from molecular structure and drug design to genomics, brain imaging, cognitive science, and clinical investigation, has given us a pool

of information that we can now use to build into therapeutic applications for all neurological diseases and disorders. As scientists, we will continue to move forward not just as individuals, exploring our particular areas of interest, but also in concert with colleagues in all areas of science, mining opportunities to collaborate across disciplines.

Public confidence in science is essential if we are to be successful in our mission. To this end we recognize that dialogue between researchers and the public will be essential in considering the ethical and social consequences of advances in brain research.

The Dana Alliance for Brain Initiatives and the European Dana Alliance for the Brain represent a community of neuroscientists willing to commit to ambitious goals, as seen in 1992 in Cold Spring Harbor, New York, where an American research agenda was set forth and again in 1997 when the newly formed European group followed suit with its own goals and objectives. Both groups now are moving to build upon gains made so far. We are setting new goals to guide what can be achieved in the near term, and project even further into the future. By allowing ourselves to imagine what benefit to humanity this new era in neuroscience is likely to bring, we can speed progress toward achieving our goals.

The Goals

Combat the devastating impact of Alzheimer's disease.

In Alzheimer's disease, a small piece of the protein amyloid accumulates and is toxic to nerve cells. The mechanism of this accumulation has been worked out biochemically and in genetic studies in animals. Using these animal models, new therapeutic drugs and a potentially powerful vaccine are being developed to prevent the accumulation of this toxic material or enhance its removal. These new therapies, which will be tried in humans in the near future, offer realistic hope that this disease process can be effectively treated.

Discover how best to treat Parkinson's disease.

Drugs that act on dopamine pathways in the brain have had significant success in treating the motor abnormalities of Parkinson's disease. Unfortunately, this therapeutic benefit wears off for many patients after 5–10 years. New drugs are being developed to prolong the action of dopamine-based treatments and to slow the selective loss of nerve cells that causes this disease. For those in whom drug therapies fail, surgical approaches, such as deep brain stimulation, are likely to be of benefit. Newer forms of brain imaging have made it possible to determine if these treatments are rescuing nerve cells and restoring their circuits back toward normal.

Decrease the incidence of stroke and improve post-stroke therapies.

Heart disease and stroke can be strikingly reduced when people stop smoking, keep their cholesterol levels low, maintain normal weight by diet and exercise, and when diabetes is detected and treated. For those with strokes, rapid evaluation and treatment can lead to dramatic improvement and less disability. New treatments will be developed to further reduce the acute impact of stroke on normal brain cells. New rehabilitation techniques, based on understanding how the brain adjusts itself following injury, will result in further improvement.

Develop more successful treatments for mood disorders, such as depression, schizophrenia, obsessive compulsive disorder, and bipolar disorder.

Although the genes for these diseases have eluded researchers over the past decade, the sequencing of the human genome will reveal several of the genes for these conditions. New imaging techniques, along with new knowledge about the actions of these genes in the brain, will make it possible to see how certain brain circuits go awry in these disorders of mood and thought. This will provide the basis for better diagnosis of patients, more effective use of today's medications, and the development of entirely new agents for treatment.

Uncover genetic and neurobiological causes of epilepsy and advance its treatment.

Understanding the genetic roots of epilepsy and the neural mechanisms that cause seizures will provide opportunities for preventive diagnosis and targeted therapies. Advances in electronic and surgical therapies promise to provide valuable treatment options.

Discover new and effective ways to prevent and treat multiple sclerosis.

For the first time, we have drugs that can modify the course of this disease. New drugs, aimed at altering the body's immune responses, will continue to decrease the number and severity of attacks of multiple sclerosis. New approaches will be taken to stop the longer-term progression caused by the breakdown of nerve fibers.

Develop better treatments for brain tumors.

Many types of brain tumors, especially those that are malignant or have spread from cancer outside the brain, are difficult to treat. Imaging techniques, focused-radiation treatments, different forms of delivery of drugs to the tumor, and the identification of genetic markers that will assist diagnosis, should provide the basis for development of innovative therapies.

Improve recovery from traumatic brain and spinal cord injuries.

Treatments are being evaluated that decrease the amount of injured tissue immediately after an injury. Other agents are aimed at promoting the rewiring of nerve fibers. Techniques that encourage cellular regeneration in the brain to replace dead and damaged neurons will advance from animal models to human clinical trials. Electronic prostheses are being developed that use microchip technology to control neural circuits and return movement to paralyzed limbs.

Create new approaches for pain management.

Pain, as a medical condition, need no longer be woefully undertreated. Research into the causation of pain and the neural mechanisms that drive it will give neuroscientists the tools they need to develop more effective and more highly targeted therapies for pain relief.

Treat addiction at its origins in the brain.

Researchers have identified the neural circuits involved in every known drug of abuse, and have cloned major receptors for these drugs. Advances in brain imaging, by identifying the neurobiological mechanisms that turn a normal brain into an addicted brain, will enable us to develop therapies that can either reverse or compensate for these changes.

Understand the brain mechanisms underlying the response to stress, anxiety, and depression.

Good mental health is a prerequisite for a good quality of life. Stress, anxiety, and depression not only damage people's lives; they can also have a devastating impact on society. As we come to understand the body's response to stress and the brain circuits implicated in anxiety and depression, we will be able to develop more effective ways to prevent them and better treatments to lessen their impact.

The Strategy

Take advantage of the findings of genomic research.

The complete sequence of all the genes that comprise the human genome will soon be available. This means that we will be able, within the next ten to fifteen years, to determine which genes are active in each region of the brain under different functional states, and at every stage in life—from early embryonic life, through infancy, adolescence, and adulthood. It will be possible to identify which genes are altered so that their protein products are either missing or functioning abnormally in a variety of neurological and psychiatric disorders. Already this approach has enabled scientists to establish the genetic basis of such disorders as Huntington's disease, the spinocerebellar ataxias, muscular dystrophy, and fragile-X mental retardation.

The whole process of gene discovery and its use in clinical diagnosis promises to transform neurology and psychiatry and represents one of the greatest challenges to neuroscience. Fortunately the availability of microarrays or "gene chips" should greatly accelerate this endeavor and provide a powerful new tool both for diagnosis and for the design of new therapies.

Apply what we know about how the brain develops.

The brain passes through specific stages of development from conception until death, and through different stages and areas of vulnerability and growth that can be either enhanced or impaired. To improve treatment for developmental disorders such as autism, attention deficit disorder, and learning disabilities, neuroscience will build a more detailed picture of brain development. Because the brain also has unique problems associated with other stages of development, such as adolescence and aging, understanding how the brain changes during these periods will enable us to develop innovative treatments.

Harness the immense potential of the plasticity of the brain.

By harnessing the power of neuroplasticity—the ability of the brain to remodel and adjust itself—neuroscientists will advance treatments for degenerative neurological diseases and offer ways to improve brain function in both healthy and disease states. In the next ten years, cell replacement therapies and the promotion of new brain cell formation will lead to new treatments for stroke, spinal cord injury, and Parkinson's disease.

Expand our understanding of what makes us uniquely human.

How does the brain work? Neuroscientists are at the point where they can ask—and begin to answer—the big questions. What are the mechanisms and underlying neural circuits that allow us to form memories, pay attention, feel and express our emotions, make decisions, use language, and foster creativity? Efforts to develop a "unified field theory" of the brain will offer great opportunities to maximize human potential.

The Tools

Cell replacement

Adult nerve cells cannot replicate themselves to replace cells lost due to disease or injury. Technologies that use the ability of neural stem cells (the progenitors of neurons) to differentiate into new neurons have the potential to revolutionize the treatment of neurological disorders. Transplants of neural stem cells, currently being done on animal models, will rapidly reach human clinical trial status. How to control the development of these cells, direct them to the right place, and cause them to make the appropriate connections are all active areas of research.

Neural repair mechanisms

By using the nervous system's own repair mechanisms—in some cases, regenerating new neurons and in others restoring the wiring—the brain has the potential to "fix" itself. The ability to enhance these processes provides hope for recovery after spinal cord injury or head injuries.

Technologies that may arrest or prevent neurodegeneration

Many conditions, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and ALS are the result of degeneration in specific populations of nerve cells in particular regions of the brain. Our present treatments, which modify the symptoms in a disease like Parkinson's disease, do not alter this progressive loss of nerve cells. Techniques that draw on our knowledge of the mechanisms of cell death are likely to offer methods to prevent neurodegeneration and, in this way, stop the progression of these diseases.

Technologies that modify genetic expression in the brain

It is possible to either enhance or block the action of specific genes in the brains of experimental animals. Mutated human genes that cause neurological diseases, such as Huntington's and ALS, are being used in animal models to assist in the development of new therapies to prevent neurodegeneration. Such techniques have also provided valuable information about normal processes, such as development of the brain, learning, and the formation of new memories. These technologies provide an approach to the study of normal and abnormal brain processes more powerful than there has ever been available before and, in time, may be used clinically in the treatment of many brain disorders.

Advanced imaging techniques

There have been remarkable advances in imaging both the structure and the function of the brain. By developing techniques that image brain functions as quickly and accurately as the brain does, we can achieve "real-time" imaging of brain functions. These technologies will allow neuroscientists to see exactly which parts of the brain are involved as we think, learn, and experience emotions.

Electronic aids to replace non-functional brain pathways

In time it may be possible to bypass injured pathways in the brain. Using multi-electrode array implants and micro-computer devices—which monitor activity in the brain and translate it into signals to the spinal cord, motor nerves, or directly to muscles—we expect to be able to offer the injured hope for functional recovery.

Novel methods of drug discovery

Advances in structural biology, genomics, and computational chemistry are enabling scientists to generate unprecedented numbers of new drugs, many of which promise to be of considerable value in clinical practice. The development of new, rapid screening procedures, using "gene chips" and other high throughput technologies, will reduce the time between the discovery of a new drug and its clinical evaluation, in some cases, from years to just a few months.

Our Commitment, Bench to Bedside

Today, neuroscience research benefits from an unprecedented breadth of opportunity. We have expanded our understanding of brain function, disease onset, and disease progression. A sophisticated arsenal of tools and techniques now enables us to apply our knowledge and accelerate progress in brain research.

As scientists, we are committed to continue making progress "at the bench." To attack major brain disorders, such as Alzheimer's, stroke, or Parkinson's, will require continued basic research from which clinicians can move toward development of new treatments and therapies. We have a responsibility to continue such research and to enlist its support by the public.

We also have the obligation to explain those areas of scientific research that soon may have direct application to human beings. To progress beyond laboratory research, we need to take the next clinical steps in partnership with the public—translating science into real and genuine benefits "at the bedside."

As our tools and techniques become more sophisticated, they may be considered threatening in their perceived potential for misuse. It is important to recognize the understandable fears that brain research may allow scientists to alter the most important aspects of our brains and behavior, changing the very things that make us uniquely human. Public confidence in the integrity of scientists, in the safety of clinical trials—the cornerstone of applied research—and in the assurance of patient confidentiality, must be continually maintained.

Putting research into a real-life context is always a challenge. People not only want to know how and why research is done, they also want to know why it matters to them. Allaying the public's concerns that the findings of brain science could be used in ways that might be harmful or ethically questionable is particularly important. Meeting both of these challenges is essential if those affected by neurological or psychiatric disorders are to reap fully the benefits of brain research.

Our mission as neuroscientists has to go beyond brain research. We accept our responsibility to explain in plain language where our science, and its new tools and techniques, are likely to take us. We, the members of the Dana Alliance and the European Dana Alliance willingly embrace this mission as we embark on a new decade of hope, hard work, and partnership with the public.

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