



The 2007 Progress Report on  
**BRAIN RESEARCH**

Introduction by David C. Van Essen, Ph.D.

**NEUROETHICS AT AGE 5**  
Essay by Steven E. Hyman, M.D.

*An online version of the Progress Report on Brain Research  
is available at [www.dana.org](http://www.dana.org).*

2007

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ON BRAIN RESEARCH**

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Published by DANA PRESS  
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The Progress Report on Brain Research is published annually in March by the Dana Alliance for Brain Initiatives, a nonprofit organization of more than 200 leading neuroscientists, including ten Nobel laureates. The Dana Alliance is committed to advancing public awareness about the progress and benefits of brain research and to disseminating information on the brain in an understandable and accessible fashion. Supported entirely by the Dana Foundation, the Dana Alliance does not fund research or make grants.

The Dana Alliance for Brain Initiatives

745 Fifth Avenue

Suite 900

New York, NY 10151

A Dana Alliance for Brain Initiatives publication

Produced and distributed by Dana Press

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ISSN: 1553-5398

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# INTRODUCTION

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by David C. Van Essen, Ph.D.  
President, Society for Neuroscience

This year's Progress Report summarizes more than 100 research discoveries that collectively illustrate how research in neuroscience is helping to better understand, diagnose, and treat many debilitating diseases and disorders of the nervous system. Each of the 10 sections focuses on discoveries related to a particular class of disorders or to a cross-cutting theme such as neuroethics. These individual discoveries ("nuggets of neuroscience"), and the broader themes that emerge from the report as a whole, are a significant part of the grand quest to understand the human brain in health and disease.

The human brain is an amazingly complex structure for processing information and controlling all aspects of our behavior. The complexity of the brain's intricate neural circuitry, involving billions of neurons and trillions of synapses, greatly exceeds that of any other organ system in the body.

This complexity is evident at many levels. At molecular and cellular levels it involves exquisitely choreographed molecular signals for transmitting information from one cell to another and for adjusting the strength of these signals during development and learning. At the systems level, it involves a symphony of coordinated neural activity patterns involving thousands of distinct brain structures communicating through tens of thousands of anatomical pathways. It also involves a high degree of individual variability in brain structure and function from one person to the next that is responsible for the tremendous diversity in our individual personalities and intellectual capabilities.

Given the brain's staggering complexity—far greater than that of a space shuttle or a supercomputer—it is hardly surprising that the nervous system can malfunction in countless ways.

Indeed, more than 1,000 disorders and diseases of the nervous system have been identified, and the list continues to grow. The most prevalent afflictions, including Alzheimer's, schizophrenia, stroke, and learning disabilities, in aggregate affect a large fraction of our population and place a staggering burden on society in terms of economic impact, distress, and human suffering.

Without major progress in preventing and treating nervous system disorders, this burden will only grow as people continue to live longer. In order to accelerate progress, we need a much deeper understanding of disease mechanisms and of the normal mechanisms of brain function and brain plasticity, or adaptability. Such advances, including those highlighted in this report, will allow us to better harness and enhance the normal capacity of the nervous system to regenerate, repair, and adapt itself to insult and injury.

Several broad themes emerge from accomplishments in brain research in 2006. One involves progress in characterizing the genetic factors contributing to a variety of neurological and psychiatric disorders. These range from the elucidation of the role played by specific genes in familial Parkinson's disease to the identification of many anxiety-related genes in a mouse model.<sup>1,3</sup>

Another powerful strategy is to combine what we know of a gene with other experimental approaches such as neuroimaging. An exciting example in this report involves using magnetic resonance imaging to characterize brain abnormalities (in both structure and function) in individuals who carry a particular genetic variation implicated in violent behavior but who have no history of psychiatric disorder.<sup>4</sup> The power of neuroimaging approaches is also evident from discoveries of distinct brain structural abnormalities in attention-deficit/hyperactivity disorder<sup>5</sup> and functional abnormalities in autism.<sup>6</sup>

Neurodegenerative diseases, including Parkinson's disease, Huntington's disease, Alzheimer's, and amyotrophic lateral sclerosis (ALS), continue to be the focus of intensive investigation in many laboratories. One set of advances involves a better understanding of the cell biology of how some proteins fail to fold into molecular configurations that make them function properly and how the normal machinery for coping with misfolded proteins may cause degeneration when it goes awry. Another approach to the problem is to use interventional strategies to deliver treatments that protect against neuronal damage and death.<sup>7</sup>

*The prospect of instituting neuronal replacement therapy has been something of a holy grail for many neuroscientists, especially because adult neurogenesis is widespread in many other species.*

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Other research continues to reveal the role of the immune system in relation to the brain. Normally the two “play well together,” but many discoveries this past year point to the devastation that can occur when the immune system is provoked to attack the brain. One arena involves inflammatory responses that aggravate the neuronal damage initiated by neurodegenerative processes in Alzheimer’s, Parkinson’s, Huntington’s, and ALS. These discoveries have led to new therapeutic strategies involving anti-inflammatory drugs to reduce neuronal damage in each of these neurodegenerative diseases.

In autoimmune diseases such as multiple sclerosis, the attack by the immune system appears to be a primary assault directly on glial cells. Discoveries in the past year have provided important insights regarding the identity of key proteins that mediate the immune attack and the identification of an antibody biomarker that may allow better regulation of certain treatments in autoimmune diseases.<sup>8,9</sup>

In the human brain, neurons that die are irreplaceable, insofar as the birth of new neurons (neurogenesis) does not occur in adults except in restricted brain regions. The prospect of instituting neuronal replacement therapy has been something of a holy grail for many neuroscientists, especially because adult neurogenesis is widespread in many other species. Hair cells in the ears’ cochlea are a particularly attractive target because they are part of a relatively simple neural circuit and because hearing loss is such a prevalent and debilitating disorder. Recent progress in characterizing genes that regulate hair cell proliferation provide hope for future progress.<sup>10</sup> Elsewhere in the brain, intensive efforts are under way to determine what regulates neurogenesis in the hippocampus and other brain regions where it takes place and to use stem cells to promote useful neurogenesis in other regions of the brain and spinal cord.<sup>11,12</sup>

*Where will brain research go from here?  
Three clear trends will strongly influence the field  
well into the future.*

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An overarching theme is that progress in diagnosing and treating brain-related diseases also can bring special challenges that have implications for ethics and health policy. Members of the Dana Alliance for Brain Initiatives have played a major role in shaping the emergent field of neuroethics. The essay on neuroethics by Steven Hyman provides a thoughtful overview of the history of this new field and of the types of issues it wrestles with. These are brought into sharper focus in the Neuroethics section of the main report, which highlights a range of issues and controversies, including topics related to brain privacy, the nonconscious brain, and the implications of neural prostheses.

Where will brain research go from here? Three clear trends will strongly influence the field well into the future:

**Technology drives discovery.** Most of the discoveries reported here simply could not have been made a decade ago, because key experimental methods such as functional magnetic resonance imaging and high-throughput gene sequencing were either nonexistent or inadequate. A wide variety of methods for acquiring and analyzing information about the brain are continually being developed by methods-oriented scientists and engineers in academia and in the private sector. Sustained investment in these efforts is critical for insuring that the pace of discovery continues to accelerate.

**Bench to bedside to bench.** “Bench to bedside” is a widely used shorthand term for the process of translating discoveries made by basic and translational neuroscientists into improved clinical care. Information flow in the reverse direction, from the clinical side back to basic neuroscience, is now recognized as very important as well. By studying diseases and disease mechanisms, neuroscientists often gain insights into fundamental mechanisms of brain function and development. For example, at all four

Presidential Lectures at the 2006 annual meeting of the Society for Neuroscience, the presenters discussed how their own research benefited from bi-directional interactions between basic and clinical neuroscience.

At a personal level, this perspective resonates very strongly because it reflects recent changes in my own research program. Whereas I was a “pure” basic neuroscientist until a few years ago, the main thrust of research in my laboratory currently focuses on specific neurological or psychiatric disorders, using novel methods for analyzing the structure and function of cerebral cortex. On a larger scale, the fastest-growing research theme at the Society for Neuroscience annual meeting is the disease theme, indicating increasing engagement on disease-related research by the neuroscience community as a whole.

**The information explosion.** The studies described in this report represent the tip of a vast and rapidly expanding iceberg of information that emerges from the neuroscience community each year. Only a fraction of the potentially useful information is published or made accessible in databases. Moreover, even that which is accessible in online journals and databases cannot be searched as easily and effectively as is desirable. This is likely to change dramatically in the coming decade as improvements in information technology open up new vistas that allow scientists, clinicians, and the lay public to access a wealth of information about the nervous system quickly, reliably, and conveniently in ways that we currently can only dream about.

# NEUROETHICS: AT AGE 5, FIELD CONTINUES TO EVOLVE

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by Steven E. Hyman, M.D.



Precisely because the brain lies at the center of our humanity and most valued capacities, brain diseases are particularly devastating and thus a focus of intense research efforts.

While science is hard at work to defeat some of the cruelest conditions that afflict humankind, it is also providing important insights into human thought, emotion, and behavior, in health as well as illness. However, new technologies that permit us to observe the workings of the human brain and to influence its function also raise critical ethical and policy questions.

Advances in brain imaging have brought us closer to a time when we can make diagnoses objectively that today must rely on clinical observation alone. Advances in genetics and molecular biology give us hope that treatments can be developed, perhaps within a decade, that will slow the progress of neurodegenerative illnesses such as Alzheimer's disease and Parkinson's disease.

Along with genetics, advances in cognitive and social neuroscience suggest new approaches to schizophrenia and autism, with the goal of returning people to full health and functioning. Progress at the interface of neuroscience with engineering points to a time when interactions between brain and computer will give meaningful motor control back to victims of paralysis. Early experiments with deep brain stimulation suggest that when we understand brain circuitry well enough, we may be able to better treat depression, anxiety disorders, and other ills affecting emotion and cognition.

Progress against diseases of the brain is and ought to be a central goal for our society. Progress will be hard-won because brains are so complex and because the highest levels of human cognition, for example, are not readily modeled in animals. But how to move

more effectively against disease, how to engage the brightest young minds in the task, and how to give them the necessary tools are not the only challenges we face.

This year is the second time the Dana Alliance's Progress Report on Brain Research has highlighted neuroethics (the first time was in 2003). Members of the Alliance have become deeply involved in writing and speaking on the ethical challenges that emerge from brain science. These concerns, emanating from the study of brain, behavior, and mental life, had been treated piecemeal in diverse venues, often in narrow communities of scientists, ethicists, and other scholars. A broad and lasting commitment to the questions that have been brought together under the term "neuroethics" was crystallized in a conference sponsored by the Dana Foundation in San Francisco entitled, "Neuroethics: Mapping the Field."

Since that meeting in May 2002, a growing number of meetings, papers, and books have nurtured a vibrant interdisciplinary field with contributions from a diverse community that includes, among others, scientists, philosophers, physicians, lawyers, sociologists, political scientists, and policy makers. Given the growing interest, a group met in Asilomar, California, in May 2006 and decided to found a Neuroethics Society ([www.neuroethicssociety.org](http://www.neuroethicssociety.org)).

The attendees at the Asilomar conference believed that a society would help form a platform to facilitate the kinds of sustained conversations that may help launch interdisciplinary fields in a way that permits scholars with different backgrounds to interact. Ever-increasing sophistication and depth, the thinking goes, will allow them to address critical problems.

This nascent society is hardly alone in bringing attention to the field. The American Association for the Advancement of Science has regularly featured neuroethics topics at its meetings. The Society for Neuroscience has featured a neuroethics lecture at its yearly conference since 2003 and has had three symposia on

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*I believe that what is driving the emergence of neuroethics is the special status of the brain.*

neuroethics, including one in October 2006 that focused on a wide range of international issues, from researchers educating volunteers and communities in poorer countries to wealthier governments formulating ethical guidelines as brain research progresses. This year the Cognitive Neuroscience Society and the Association for Psychological Science will feature symposia on neuroethics. The Wellcome Trust Bioethics Summer School has focused on neuroethics for the past two years. The American Academy of Arts and Sciences is planning a symposium on the use of neuroimaging in lie detection for early 2007.

Despite this growth, opportunities to publish are only now beginning to increase. New interdisciplinary fields often find difficulty in publishing for two reasons. First, the work may not align perfectly with the work of existing disciplines that control scholarly journals. Second, when a field requires significant contributions from multiple disciplines in order to succeed, finding relevant source material can be challenging. Neuroscientists, lawyers, and philosophers often do not know where to look in order to find articles dealing with problems in neuroethics.

Several efforts are therefore under way to provide venues for publication. The Neuroethics Society has formed an alliance with the American Journal of Bioethics to create special issues (American Journal of Bioethics–Neuroscience) dedicated to the field, and the Journal of Cognitive Neuroscience is expanding its coverage.

In these early days of neuroethics, one question that keeps emerging is why a new field is required at all. Why does the larger tent of bioethics not suffice? Of course, many scholars involved in neuroethics remain—and should remain—firmly rooted in existing bioethics activities. Many neuroethical concerns are central considerations of bioethics: informed consent given by individuals with cognitive impairment or end-of-life clinical issues, for example.

But brain research calls for something more. I believe that what is driving the emergence of neuroethics is the special status of the brain; a deep consideration of the implications of brain research pushes us well beyond the usual boundaries of bioethics.

The potential use of brain imaging to reconstruct a person's recent experience or to investigate his or her veracity not only

*Even more unique to neuroethics is the recognition that the brain is not only the object of ethical study, but also the basis of our ethical principles.*

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raises traditional bioethical questions of privacy but also engages broader communities—including law enforcement and national security experts—who are not often represented within discussions of bioethics.

Similarly, efforts to influence or control brain function only partly overlap with ethical concerns raised by attempts to alter the function of the heart or kidney. That is because the control of brain function goes to the core of our selfhood and autonomy. Even more unique to neuroethics is the recognition that the brain is not only the object of ethical study, but also the basis of our ethical principles.

This latter point is in itself contentious for those who believe that there is natural law or divine guidance on ethical principles. In a country such as the United States, in which religion is important, that discussion remains vital and significant. Moreover, as we begin to understand the neural foundations of social interaction including such issues as prejudice and trust, and as ways of influencing such interactions emerge (e.g., by pharmacology or electrical stimulation), profound questions arise about where our different ethical systems come from. Are they derived from timeless, rational principles, contingent products of an evolving brain, or both? If we are to handle scientific progress in the most adaptive way, neuroethics is here to stay.

PROGRESS IN  
BRAIN RESEARCH  
IN 2006

# DISORDERS THAT APPEAR IN CHILDHOOD



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Among several significant studies involving childhood in 2006, scientists pinpointed specific areas of the brain that contribute to enlarged brain size, which commonly occurs in autism spectrum disorder. Researchers also gained new insights into some of the neuroanatomical and biochemical differences that appear to be responsible for the cognitive difficulties experienced by children with attention-deficit/hyperactivity disorder, and more evidence emerged regarding the role of viral infections in developmental disorders such as cerebral palsy.

### ***Brain Abnormalities in Autism***

Autism spectrum disorder (ASD), a grouping that includes autism and disorders similar to it, is a pervasive developmental disorder manifested primarily in greatly diminished social interaction and communication skills. No one knows exactly what causes ASD, but scientists have identified many neurological abnormalities that might contribute to the social and cognitive deficits typically observed in ASD.

Abnormal activity in specific brain regions has been associated with ASD. For example, a part of the brain called the inferior frontal gyrus was markedly less active in children with ASD during the performance of certain tasks related to social interaction, according to a research team led by Marco Iacoboni, a neuroscientist at the University of California, Los Angeles.<sup>1</sup>

In a study reported in *Nature Neuroscience*, Iacoboni's team used functional magnetic resonance imaging to investigate neural activity of 10 high-functioning children with ASD and 10 normally developing children as the children observed and imitated facial emotional expressions. The degree of reduced activity correlated with the severity of their symptoms.

The inferior frontal gyrus is believed to be part of the so-called mirror neuron system, which plays an important role in the perception and expression of emotions and enables individuals to experience empathy. The findings indicate that a dysfunctional mirror neuron system may underlie the social deficits observed in autism.

Abnormalities in brain size also have been associated with ASD. In a study published in the *American Journal of Psychiatry*, a group of researchers led by Antonio Hardan, a Stanford University psychiatrist, used magnetic resonance imaging scans to compare the size of the cortex (the outer layer of the brain) between 17 children with autism and 14 children without the disorder.<sup>2</sup> Cortical thickness is a sensitive index of normal brain development.

Although the meaning of cortical thickness at the level of individual cells is unknown, the researchers believe it may indicate the degree of "arborization," the branching of brain cell connections. During normal brain development, a massive overproduction of cells and these connections (synapses) to other brain cells occurs. A competitive elimination, or "pruning," of neurons and these connections follows. The scientists hypothesize that this pruning results in cortical thinning.

When the investigators analyzed the brain images, they found increased cortical thickness in the brain's temporal and parietal lobes of children with autism. They suggest that these anatomical differences are partly responsible for the increased brain size in ASD.

These findings will lead the scientists to look at what normally controls the thinning of the cortex—including genetic influences. They plan to investigate the different genes that are involved in this process, with the hope of finding an association that will help them better understand what causes thicker brain structures in autism, which might lead to new treatments.

An enlarged amygdala also appears to contribute to the increased brain size observed in autism, according to a study published in *Archives of General Psychiatry*.<sup>3</sup> The amygdala is a part of the brain that plays an important role in socio-emotional functioning. In this study, researchers led by Stephen Dager of the University of Washington used magnetic resonance imaging to measure amygdala size in 45 children with ASD between the ages of 3 and 4.

The investigators found that an enlarged amygdala—particularly its right side—was associated with symptom severity in these children. Moreover, when the researchers tested the same



### Investigating autism

*Researcher Stephen Dager, foreground, checks a brain scan as he and Dennis Shaw conduct research to measure amygdala size in children with autism spectrum disorder.*

children about 3 years later, they found that the children with a greater degree of right amygdala enlargement had poorer development of language and social skills.

These results strongly implicate amygdala abnormalities in the behavioral impairments found in autism, and they also suggest that the size of the right amygdala might be used to predict the clinical course of the disease.

In a more recent paper, published in *Neurology*, researchers from the same laboratory reported that the disabilities found in children with autism, compared to children with developmental delay, may be attributable to increased "transverse relaxation" of brain cells (gray matter) in the brain.<sup>4</sup> Transverse relaxation, as measured by magnetic resonance imaging (MRI), is a measure of how tightly bound brain cells are, as measured by the extent to which they displace water in the brain. This technique is used to measure brain maturation over time.

The investigators compared 60 children with autism to 16 with developmental delay and 10 who were developing normally. All of the children were between 2 and 4 years old. They

*Scientists have long suspected that having too little dopamine might produce ADHD. Recent evidence suggests that this is the case.*

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found that cells were significantly more tightly bound in normally developing children, compared with children with autism. Children with developmental delay fell between the normally developing children and those with autism in terms of how tightly the cells were bound.

Autism remains a mysterious disease. These imaging studies suggest developmental abnormalities in the formation of neuronal structures, perhaps early in gestation.

## ***New Insights into ADHD***

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder with consequences that diminish academic and occupational achievement and increase the risk of depression, substance abuse, and accidental injury or even death. ADHD is characterized by restlessness and distractibility, believed to be caused by an impaired ability to inhibit certain impulses inside the brain.

ADHD can, in most cases, be successfully treated with medications that increase the availability of an inhibiting neurotransmitter, called dopamine, inside the brain. Scientists have long suspected that having too little dopamine might produce ADHD. Recent evidence suggests that this is the case and points to defects in “dopamine transporters” in the brain as the main culprit: the transporters take up too much dopamine before it can be passed from one brain cell to another.

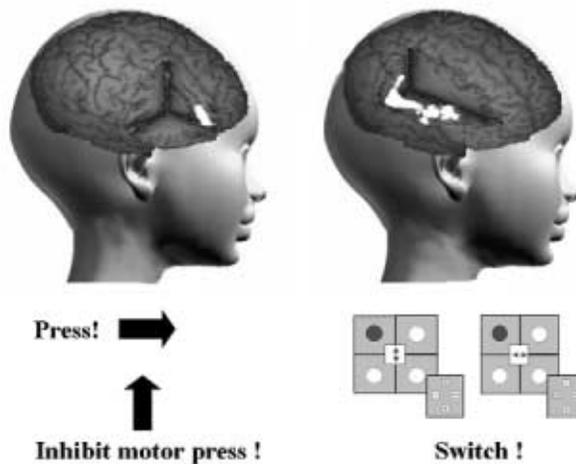
A research team led by Donald Gilbert, a pediatric neurologist at Cincinnati Children's Hospital Medical Center, tested how the brain's motor cortex inhibits movement in 16 children and adolescents with ADHD, both before and after they were given medications that increase the availability of dopamine inside the brain.<sup>5</sup>

The resultant increased amounts of dopamine inhibited motor cortex activity in all children tested, but the medicine had a much

greater effect in children with a genetic variation called DAT1, which ordinarily causes too much dopamine transporter activity. The result is too little inhibitory dopamine. This research implicates genetically altered dopamine transporters in ADHD.

In a related development, Katya Rubia of the Institute of Psychiatry at King's College in London and colleagues found similar deficiencies in brain regions responsible for motor inhibition and switching of behavior in a group of 19 boys with ADHD who had never taken any medication for the disorder.<sup>6</sup> This is significant, the researchers point out, because previous research has been undertaken in children who had been taking ADHD medications, which might have confounded the results.

Using functional magnetic resonance imaging, Rubia's team found abnormal brain activation in these "medication-naive" children and adolescents with ADHD during tasks that involved motor inhibition and task switching (which requires cognitive flexibility). The finding suggests that underactivation in this patient group is unrelated to long-term stimulant exposure. Underactivation was evident during both tasks in prefrontal brain regions, as well as in temporal and parietal regions, which



### Brain activation in ADHD

*Children with attention-deficit/hyperactivity disorder showed reduced brain activation in the medial prefrontal cortex when they had to inhibit a motor response, left, and in frontotemporal brain regions when they had to switch tasks, right.*

*Brain thickness as an indicator of brain development has been studied in ADHD, just as it has been studied in autism.*

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in the past have not been implicated in ADHD.

Brain thickness as an indicator of brain development has been studied in ADHD, just as it has been studied in autism. National Institute of Mental Health researchers led by Philip Shaw measured cortical thickness in a group of 166 children with ADHD.<sup>7</sup> The researchers obtained magnetic resonance images approximately every two years in these children and compared them with scans of healthy children.

An analysis of the images revealed that children with ADHD had a thinner cortex in parts of the brain that are important for the control of attention. Subsequent scans of these children revealed that those with worse clinical outcomes had a particularly thin cortex at the front of the brain, near a region that controls aspects of attention, such as inhibiting inappropriate behaviors.

Moreover, the children with ADHD who had better clinical outcomes showed a distinctive pattern of cortical change in the right parietal cortex, which controls some of the most fundamental aspects of attention. Here, by late adolescence, the cortex reached the same thickness in these children as in healthy children. However, this "normalization" did not occur in the children with worse clinical outcomes. These results were unaffected by whether the children had been taking medication for ADHD.

This work gives a very detailed picture of the cortex in children with ADHD and highlights brain changes that may reflect, or even drive, recovery from the disorder, the researchers suggest.

As in autism, imaging studies are suggesting what is going wrong in brain functions in ADHD. These types of studies may be useful in both diagnosis and treatment.

### ***Cerebral Palsy: The Role of Infections***

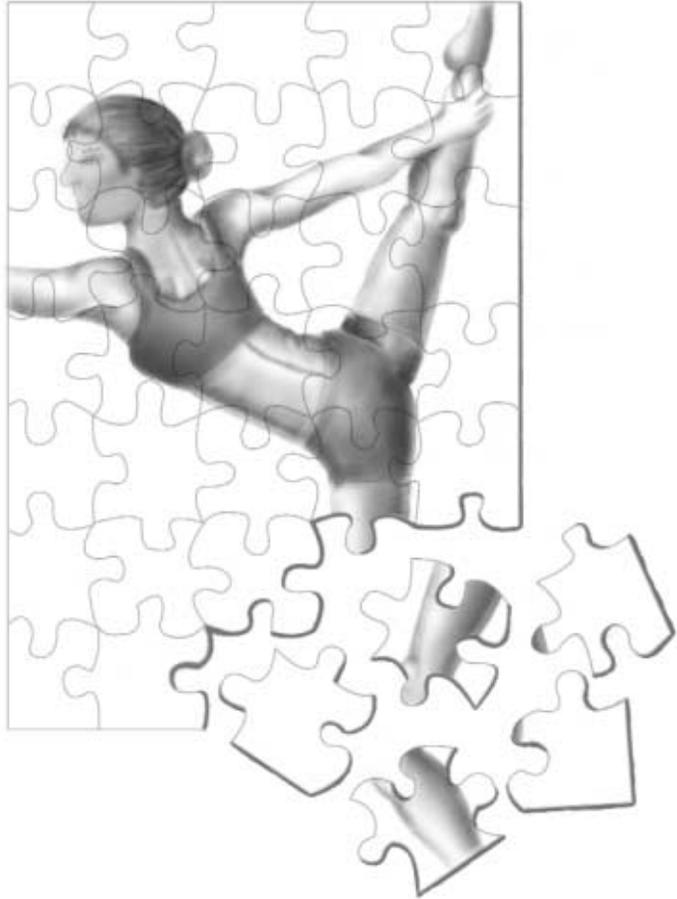
Researchers uncovered more evidence in 2006 that highlights the importance of infections in developmental disorders such as cere-

bral palsy. Cerebral palsy is a permanent and often serious brain disorder, detectable from early childhood, which causes abnormal control of body movement or posture. The causes of cerebral palsy are largely unknown, and currently it cannot be prevented.

In a paper published in the *British Medical Journal*, Catherine Gibson at the University of Adelaide, Australia, and her team reported investigations into whether certain viral infections might be associated with cerebral palsy.<sup>8</sup> The researchers tested neonatal dried blood samples from 443 babies with the disorder and 883 babies without it for herpes viruses, a group of viruses that includes those responsible for chicken pox and cold sores.

The results showed that significantly more of the babies with cerebral palsy were exposed to herpes viruses during their mother's pregnancy than those without it, suggesting that these viruses may be involved in development of the disorder during pregnancy. These studies will need to be confirmed with other populations.

# MOVEMENT AND RELATED DISORDERS



**Protein Misfolding: Friends or Enemies?** 20

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Researchers made progress in 2006 along the long road from basic research to new treatments for diseases related to human movement. Laboratory studies of protein folding, inflammation, growth factors, and genetics have suggested new ways to monitor and treat these disorders. Some treatments are now being tested in animals and humans

### ***Protein Misfolding: Friends or Enemies?***

A protein's shape determines what it does in the body. Cells make proteins composed of long strings of subunits called amino acids, which coil and fold to form three-dimensional shapes. Incorrectly folded proteins do not interact properly with other proteins. Misfolded proteins may also attach to each other and form clumps called inclusions, which are common in the brains of people with some neurological disorders.

Alpha-synuclein is a major component of the inclusions (called Lewy bodies) typically found in brain cells of people with Parkinson's disease, a disorder that causes rigidity, tremors, and slow movement. Lewy bodies are also found in a related form of dementia called, appropriately, dementia with Lewy bodies. Alpha-synuclein-rich inclusions are also found in multiple system atrophy, which may resemble Parkinson's disease and cause problems with speech, balance, and coordination.

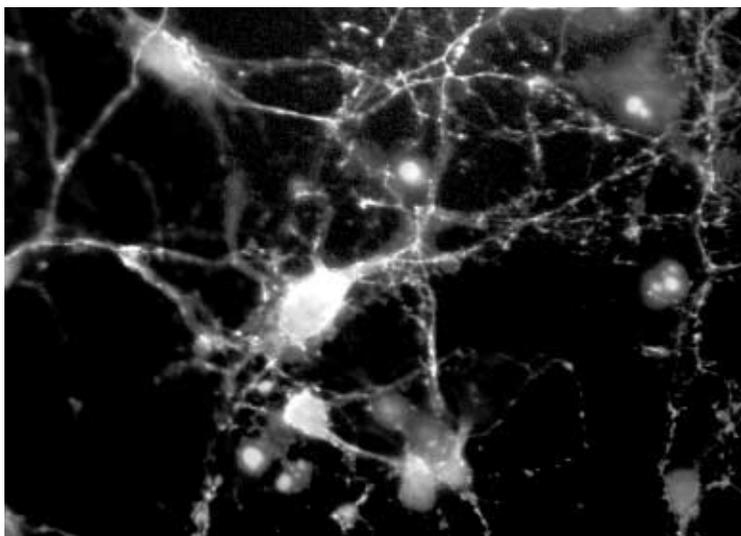
Two recent studies, by Thomas Südhof and colleagues (reported in *Cell*) and by Tracey Dickson and colleagues (reported in *Experimental Neurology*), suggest that the normal function of alpha-synuclein is to protect nerve cells from damage.<sup>1,2</sup> Normal levels of properly folded alpha-synuclein, then, seem to protect cells, but overproduction, misfolding, and aggregation of the protein are associated with disease. How?

Although there is some controversy on the issue, it is generally believed that protein misfolding and aggregation contribute to cell death, but the process remains unclear. It may be that the misfolded proteins are unable to do their normal jobs, but they also appear to interfere with the cell's other functions. A study led by Richard Morimoto, reported in *Science*, suggests that an

excess of misfolded proteins can overwhelm the cell's "quality control" system, resulting in misfolding of other proteins.<sup>3</sup> Another study, by Susan Lindquist and colleagues and published in *Science*, suggests that excess alpha-synuclein interferes with the movement of proteins within cells.<sup>4</sup>

Based on the hypothesis that inclusions contribute to cell damage, some therapies are being developed to prevent aggregation and inclusions. In contrast, a team led by David Housman and Aleksey Kazantsev tried the opposite approach, according to their report in *Proceedings of the National Academy of Sciences*.<sup>5</sup> They suspected that aggregation of misfolded proteins might be the cell's way of protecting itself from the damaging effects of misfolded protein and that inclusions might protect cells instead of damaging them. When they tested a drug they called B2, which promotes inclusion formation, they found that it actually reduced cell damage in cellular models for Huntington's disease and Parkinson's disease.

In a commentary appearing in *Experimental Neurology*, Mark Cookson offered an explanation for the apparent paradoxical effects of alpha-synuclein.<sup>6</sup> He proposed that normal, modest



### A cell's defense?

*A stressed cell, center, makes more alpha-synuclein, a protein in the brain, possibly to protect itself from the damaging effects of misfolded proteins in neurodegenerative diseases such as Parkinson's.*

*Some people may have immune responses that contribute to both allergies and Parkinson's disease.*

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levels of alpha-synuclein protect nerve cells. As the cell is stressed, it makes more alpha-synuclein in an attempt to protect itself from damage. Alpha-synuclein begins to form small aggregates, which interfere with normal cellular function. If the smaller aggregates can be clumped together into inclusions, they are prevented from damaging the cell. A better understanding of the role of misfolded proteins in neurodegenerative disease will help guide development of new drugs to prevent that damage.

### ***Inflammation and Parkinson's Disease***

In Parkinson's disease, a specific population of nerve cells dies prematurely. The question is why. One possibility is that inflammation, a clustering of reactive cells, may play a role. James Bower and his fellow researchers at the Mayo Clinic College of Medicine compared the medical records of 196 patients with Parkinson's disease to 196 matched controls. In the study, published in *Neurology*, they found that patients who went on to develop Parkinson's disease were more likely to have asthma, allergic rhinitis, or hay fever than controls.<sup>7</sup>

These findings suggest that some people may have immune responses that contribute to both allergies and Parkinson's disease. Along these same lines, Bower's group also found that drugs that block inflammation, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may have protective effects—that is, those who take NSAIDs may be less likely to get Parkinson's disease.

Together, this research helps link inflammation with Parkinson's disease, although more study is needed to determine how the two are related. Understanding the nature of this link may provide important new insights into the disease process and suggest new treatment strategies.

A group led by Miguel Hernán published a similar study in *Neurology*.<sup>8</sup> They found that men who used non-aspirin NSAIDs (such as ibuprofen) were 20 percent less likely to develop Parkinson's disease, while women who used NSAIDs were 20 per-

cent more likely to develop Parkinson's disease than people who did not use these drugs. The sex difference was unexpected and supports the findings of some other studies in which the risk factors for Parkinson's disease were different for men than for women.

Another study has shown that an antibiotic used to treat acne since the 1970s inhibits inflammation and protects neurons. Raymond Swanson and colleagues at the University of California and Veterans Affairs Medical Center in San Francisco used laboratory cultures of neurons to study how the antibiotic, minocycline, might protect neurons.<sup>9</sup> In a study published in *Proceedings of the National Academy of Sciences*, they showed that minocycline inhibits PARP-1, a protein that responds to DNA damage by promoting inflammation and cell death. They concluded that minocycline's inhibition of PARP-1 may confer its anti-inflammatory and neuroprotective effect.

Minocycline's ability to inhibit inflammation and protect neurons might have some clinical benefit, and studies in animal models of Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease) have had promising results. The results of a preliminary clinical trial published in *Neurology* suggested that minocycline might be a candidate for further clinical trials in Parkinson's disease.<sup>10</sup> Clinical trials are also under way to study minocycline in Huntington's disease and ALS.

## The Genetics of Parkinson's Disease

Familial Parkinson's disease represents about 10 percent of cases of the disease, and mutations in at least five genes are known to be involved in inherited forms of the disorder. By studying these genes, researchers have gained insights into the disease process, which might benefit all Parkinson's patients.

Two studies published in *Nature* examined the relationship between two different genes implicated in inherited Parkinson's disease.<sup>11, 12</sup> The genes, called *parkin* and *PINK1*, were shown to work together to maintain the function of mitochondria, the power plants of the cell. These studies and others provide further evidence for the longstanding belief that defects in mitochondrial function could contribute to Parkinson's disease.

**People with just one defective copy of *PINK1* had a higher risk of developing Parkinson's disease than their relatives with two normal copies of the gene.**

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The association of *parkin* and *PINK1* mutations with Parkinson's disease was first described in individuals in whom both copies of the *parkin* gene or both copies of the *PINK1* gene were defective. Although people with a single defective copy may pass it on to their children, the clinical significance of having one defective copy was unclear. A pair of studies published in *Archives of Neurology* and one published in *Movement Disorders* showed that a single defective copy could affect the development of Parkinson's disease.<sup>13-15</sup>

People with just one defective copy of *PINK1* had a higher risk of developing Parkinson's disease than their relatives with two normal copies of the gene. Similarly, people with one defective copy of *parkin* developed Parkinson's disease at a younger age than most people who develop the disease, including relatives with two normal copies. Because having one defective copy of a gene is much more common than having two defective copies, these mutations may affect more people than previously thought.

### **Monitoring and Treating Huntington's Disease**

Huntington's disease is a genetic disorder that develops in adulthood, usually between ages 40 and 50. It is characterized by progressive, uncontrolled movements; emotional disturbances; and loss of intellectual function.

Each child of a parent with Huntington's disease has a 50 percent chance of inheriting the disease gene, and a test can now predict with high accuracy whether a person has indeed inherited it. But many at-risk people choose not to be tested because there is no cure, no means of prevention, and few effective treatments for symptoms.

A potential way to monitor both the progression of the disease and effectiveness of possible treatments may be provided by monitoring immune "microglial" cells. These cells may con-

tribute to the disease by becoming activated and secreting inflammation-promoting substances. A group of investigators led by Paola Piccini used positron-emission tomography to show that the level of microglial activation correlates with the severity of Huntington's disease. These findings, published in *Neurology*, support a role for microglia in the disease.<sup>16</sup> The findings might pertain to other neurodegenerative disorders as well.

A potential treatment for Huntington's disease is glial-derived neurotrophic factor, or GDNF. It can protect nerve cells and even promote their regrowth. Despite the earlier discontinuation of a major clinical trial in humans of GDNF, smaller studies in 2006 looked at GDNF as a treatment for Parkinson's disease, with varying results.<sup>17-19</sup> GDNF was also used to treat Huntington's disease in a mouse model in a study published in *Proceedings of the National Academy of Sciences*.<sup>20</sup> Researchers led by Jeffrey Kordower used a virus to deliver GDNF into the brains of the mice, resulting in behavioral improvements, fewer dead nerve cells, and fewer inclusion bodies. Further studies are needed to determine if GDNF can be an effective treatment for Huntington's disease in humans.

Although there are currently no therapies to treat the underlying disease process, drugs that alleviate the symptoms of Huntington's disease may improve the quality of life for these patients. A clinical trial of one such treatment was reported in *Neurology*.<sup>21</sup> In this 12-week study, patients who received a drug called tetrabenazine had a significant reduction of uncontrolled movements when compared to patients who received a placebo.

# NERVOUS SYSTEM INJURIES



**Harnessing Thoughts** 27

**Spinal Cord Repair** 28

**Stroke Research** 30

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The common theme that arises from central nervous system (CNS) injury research is how basic studies can inform the development of therapies. In each of the primary CNS injuries—spinal cord injury, stroke, and brain tumors—treatments are lacking, in large part because of the complexity of the underlying processes.

Research has therefore mainly focused on unraveling the processes of cell death, nerve regeneration, and tumor genesis, with the ever-present goal of translating that knowledge into molecularly targeted treatments that prevent or repair nervous system damage.

## Harnessing Thoughts

In one of the year's biggest headline grabbers, a paralyzed man controlled a computer using thoughts. This advance is the culmination of decades of basic research on the brain's motor control center (also discussed in the Neuroethics section, page 36). A pilot study on this one patient, reported in *Nature* by John Donoghue of Brown University and a Harvard-based team of

### Brain-computer interface

*In a pilot study, a brain-computer interface allowed a single patient with paralysis to operate a computer using only his thoughts. Paired with a muscle stimulator system, such technology may one day allow people who are paralyzed to move their limbs again.*



collaborators, proved the concept that a brain-computer interface can record neural activity from a person's primary motor cortex and translate it into specific actions on external devices.<sup>1</sup>

The man in the study, paralyzed from the neck down in a spinal cord injury three years ago, was able to open e-mail messages, operate a television and light switches, open and close a prosthetic hand, and perform rudimentary actions with a multi-jointed arm. The work represents an early step toward thought-powered robotics, which are envisioned as tools to help restore some degree of independence to people paralyzed by central nervous system damage. The authors were careful to note that the technology requires further refinement before it can be practically applied beyond a research setting.

## **Spinal Cord Repair**

The many aspects of spinal cord injury require correspondingly diverse approaches to treatment, and researchers are just beginning to combine different therapeutic strategies in animal studies. Researchers continue to wrestle with fundamental difficulties in coaxing axons, the nerve fibers that transmit brain signals from cell to cell, to regenerate. The challenges include figuring out how to induce severed nerve fibers to regrow in the right directions and reconnect to the right targets to reestablish neuronal communication.

Problems that compound these difficulties include the physical gap produced by a break or crush injury to the spinal cord, the development of an impenetrable "glial scar" at the injury site, the presence of inhibitory molecules in the scar and spinal cord that block regrowth of axons (communication cables), and the complicated dynamics of guiding axons. Research is focusing on identifying and testing substances that might counteract these built-in inhibitors of axonal growth.

One substance being tested is a naturally occurring bacterial enzyme, chondroitinase ABC, which has been shown in previous research to stop inhibitory molecules called proteoglycans from forming in the glial scar. James Massey and colleagues at the University of Louisville reported in the *Journal of Neuroscience* that injecting chondroitinase into the brain stem of rats with cer-

*Studies are helping to identify the basic biological processes that drive axons to grow and connect properly.*

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vical spinal injuries promoted nerve sprouting at the injury site, confirming earlier reports.<sup>2</sup>

Researchers at Johns Hopkins and the University of Michigan, led by Ronald Schnaar and reporting in *Proceedings of the National Academy of Sciences*, also found that chondroitinase ABC induced axon growth in an animal model of spinal cord injury. They also discovered a second bacterial enzyme, sialidase, which appears to double axonal growth in rats with nerve injuries.<sup>3</sup>

In addition to helping overcome the innate inhibitors of axon regrowth, researchers are working to identify the basic biological processes that drive axons to grow and connect properly. Three research groups reported preliminary results in this area in 2006.

Yuqin Yin and Larry Benowitz of Children's Hospital Boston reported in *Nature Neuroscience* that they had discovered a naturally occurring growth factor, oncomodulin, that increased nerve regeneration five- to seven-fold when given to rats with injuries to the optic nerve.<sup>4</sup> From the Salk Institute laboratory of Samuel Pfaff comes evidence, reported in *Neuron*, that a different type of growth factor, fibroblast growth factor, actively lures growing axons to reconnect with the right cell targets in muscles.<sup>5</sup> And researchers at Yale led by Paul Forscher wrote in *Nature Cell Biology* that they identified novel functions for a molecular "motor" protein, myosin-II, that helps direct nerve growth at the tip of the axon.<sup>6</sup> These reports shed new light on how processes involved in nervous system development might be harnessed for regenerating nerves after an injury.

Elsewhere, a research group led by Jerry Silver at Case Western Reserve University used chondroitinase ABC in combination with a "neural bridge" to facilitate axon regrowth across a spinal cord injury in a rat model. The team first transplanted a segment of the animal's sciatic nerve into the gap created by the injury. This transplant formed a bridge across which newly sprouting axons could grow.

Next, they delivered a steady dose of chondroitinase ABC enzyme via an implanted pump to promote sprouting and prevent further scarring at the injury site. These rats had markedly improved mobility compared to rats that underwent the same procedure but received an inactive saline solution rather than chondroitinase ABC. The latter rats showed no new axon growth or any improvement in movement. The results appeared in the *Journal of Neuroscience*.<sup>7</sup>

Researchers at Johns Hopkins University led by Douglas Kerr took a similar approach. They transplanted motor neurons into animals with spinal cord injury, then treated the area with a cocktail of chemicals designed to overcome signals that inhibit axon growth. Next they infused a nerve growth factor that guides axons to make the right connections. The result, reported in *Annals of Neurology*, was a partial restoration of function in the paralyzed animals.<sup>8</sup>

These preliminary reports in animal models of spinal cord injury are helping to define potential approaches that one day may be used in humans.

## **Stroke Research**

The number of new strokes each year has decreased dramatically during the past few decades, thanks to drugs that lower the two major risk factors: hypertension and cholesterol.

For those who experience a stroke from a blood clot (ischemic stroke), tissue plasminogen activator (tPA), if given within three hours of stroke onset, helps to dissolve the clot and may be effective in minimizing damage. But acute treatment with tPA is grossly underutilized in current practice, in part because so few eligible patients reach a stroke unit within the requisite three hours of symptom onset.

Data from a statewide stroke registry in Minnesota found that only 2 percent of patients with blood clots received tPA. Among patients who did not receive tPA, 41 percent arrived at the hospital beyond the three-hour therapeutic window and another 38 percent could not specify a time of symptom onset. Mathew Reeves of Michigan State University led the Minnesota registry study, which was reported in *Neurology*.<sup>9</sup>

## *The emphasis is still on the development of “clotbusting” agents with a longer time window.*

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These studies demonstrate the need for development of therapies that can effectively improve brain function and recovery even if they are not administered within three hours of ischemic stroke onset.

Initial steps on this front come from clinical trial results of a neuroprotective drug designed to limit brain damage following acute ischemic stroke. Although neuroprotective drugs have been in development for two decades, this compound, NXY-059, is the first drug candidate to be developed in accordance with new expert standards designed to advance clinical stroke research. When administered within six hours of acute ischemic stroke onset, the drug reduced the rate of disability at 90 days after the stroke. However, no improvements were observed in neurological function, according to Warren Wasiewski of the Western Infirmary in Glasgow, Scotland, the principal investigator for the multisite study, which was reported in the *New England Journal of Medicine*.<sup>10</sup> The emphasis is still on the development of “clotbusting” agents with a longer time window.

### **Brain Tumors**

Deadly brain tumors called gliomas remain resistant to therapies, and patients usually die within two years of diagnosis. Scientists still have few leads about how these tumors arise and how to prevent or treat them.

Basic neuroscience investigations into glioma genesis have focused heavily on the connection between stem cells and brain tumor cells, expanding earlier research on whether stem cells may produce substances that promote cancer growth. Jeremy Rich and colleagues at Duke University wrote in *Cancer Research* about a specific type of glioma cell, which they called a “stem-cell-like glioma cancer cell” because of its shared characteristics with normal stem cells.<sup>11</sup>

The researchers examined how this type of glioma cell fuels tumor growth. They found that the cells produce large amounts

of a natural substance called vascular endothelial growth factor (VEGF), which promotes formation of blood vessels that carry oxygen and nutrients to the glioma cells to foster their growth and proliferation.

Meanwhile, work by scientists at the National Institute of Neurological Disorders and Stroke and the National Cancer Institute, led by Howard Fine and reported in *Cancer Cell*, implicates a growth factor called stem cell factor (SCF) as a key contributor to tumor growth.<sup>12</sup> Like VEGF, SCF also seems to drive cancer progression by setting up a local environment supportive of blood vessel formation. An important therapeutic strategy is to find ways to starve tumors of blood and oxygen by blocking blood vessel growth around a tumor.

Researchers also are investigating potential therapeutic roles for stem cells in treating glioma. As a team led by Arturo Alvarez-Buylla at the University of California, San Francisco, wrote in *Neuron*, a signaling molecule that regulates brain cell development in adults causes invasive tumorlike growths in mice when the molecule is abnormally stimulated, while removing the stimulation causes the tumors to regress.<sup>13</sup> This suggests a possible treatment strategy of inhibiting malignant gliomas by blocking the signaling pathway.

# NEUROETHICS



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**Nuances of Nonconscious States** 37

The field of neuroethics took on a more explicit form in 2006 with the establishment of the Neuroethics Society. Founded by eminent scientists, lawyers, and ethicists, the society hosts a Web site, [www.neuroethicssociety.org](http://www.neuroethicssociety.org), and two “partner” publications, the *American Journal of Bioethics* and the *Journal of Cognitive Neuroscience*.

The year also saw significant advances (accompanied, of course, by much debate) in four main areas of neuroethics: intervening in emotional and behavioral disorders, brain privacy, the impact of emerging technologies, and subtle changes in our understanding of nonconscious brain states such as the persistent vegetative state.

### **Placebos in Clinical Trials**

An area of ethical concern is the use of placebos in clinical trials. A debate was recently spurred by a study by Sumant Khanna in the *British Journal of Psychiatry* in which some 12 dozen patients with mania received a placebo instead of treatment with the conventional antipsychotic drug risperidone.<sup>1</sup> Some doctors have questioned the validity of the informed consent given by the study participants, says Ganapati Mudur, writing in the *British Medical Journal*.<sup>2</sup> These studies raise the issue of the ability of those with mood disorders to give informed consent.

### **Brain Privacy**

The push for ever-more-sophisticated brain imaging techniques continues to challenge old notions about the mind, such as the inviolability of an individual’s unspoken thoughts. Entrepreneurial scientists have developed lie-detecting devices based on functional magnetic resonance imaging, or fMRI, that they claim will offer

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***Feroze Mohamed and colleagues identified eight brain areas that showed significantly more activity during the act of deception than in a neutral situation, and two areas that showed significantly more activity during truth-telling than in a neutral situation.***

greater accuracy than the traditional polygraph, which measures the responses of the sympathetic nervous system.

In an fMRI study designed to simulate the investigation of a shooting inside a hospital, Feroze Mohamed and colleagues identified eight brain areas that showed significantly more activity during the act of deception than in a neutral situation, and two areas that showed significantly more activity during truth-telling than in a neutral situation. They published their work in *Radiology*.<sup>3</sup>

To date, most neuroscientists are reserving their opinions, but an editorial in *Nature* urges the neuroscience community to voice its doubts loudly and clearly, as well as to get ready for a long public debate on the ethical implications of this technology and on the nature of privacy itself.<sup>4</sup>

A new technique for examining neuroimaging data, called pattern classification, is also making it possible for scientists to predict with some accuracy what a subject is viewing, even before the subject is aware of it. Although this ability may conjure up a disturbing image of mind reading, any attempt to use pattern classification to detect lying, for example, is subject to the same limitations as a conventional polygraph, such as noise introduced by emotional responses, according to an editorial in *Nature Neuroscience*. The impact of pattern classification techniques is more likely to come at the level of basic research, where it will begin to show scientists “not just where in the brain information is processed, but how.”<sup>5</sup>

Another area of interest is the attempt to identify biological markers, such as brain abnormalities or specific genetic mutations, that suggest a tendency toward violence. A thoughtful review by Nigel Eastman and Colin Campbell in *Nature Reviews Neuroscience* questions whether causation, in the legal sense of the term, can be established by such markers, and, if so, whether a person with one or more of these biomarkers can properly be held in detention preventively, to protect the public from future harm.<sup>6</sup>

## **Emerging Technology and the Human Brain**

A unique clinical trial in which brain meets computer is that of BrainGate, a custom-developed prosthetic arm and hand used by research participant Matt Nagle, the cover feature of the July

13 issue of *Nature* (also discussed in the Nervous System Injuries section, page 27). Nagle, tetraplegic from an injury that severed his spinal cord, activates the device purely by thought—that is, by brain signals representing his intention to extend his arm, open and close his hand, and so on. The movement signals that Nagle’s conscious brain sends are picked up by a 96-electrode array implanted in his motor cortex, decoded, and transmitted to drive the movements of the prosthesis.

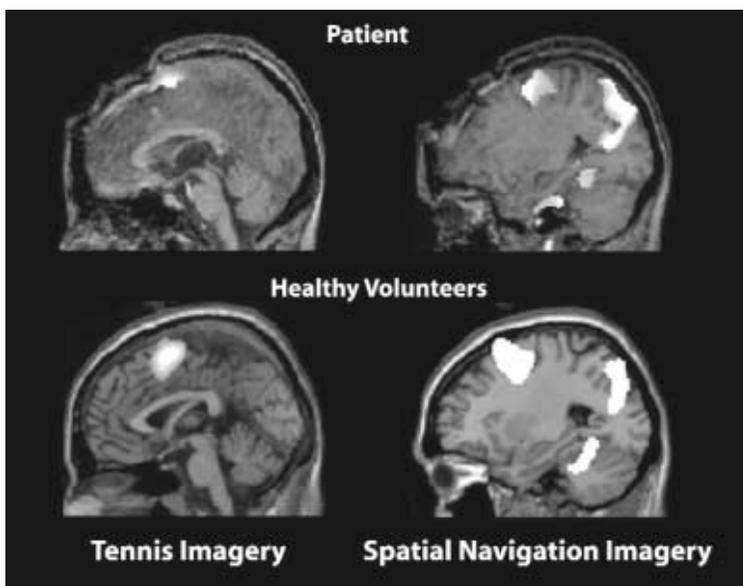
In contrast to several other types of assistive technology for patients with multiple paralysis, such as one that is driven by electrical activity on the scalp or that relies on eye movements, this neuromotor prosthesis does not call for months of training or require the user’s full attention. For instance, Leigh Hochberg and colleagues report in *Nature* that Nagle is able to carry on a conversation while opening simulated e-mail or moving the robotic hand or arm.<sup>7</sup>

An increase in the information-processing speed, and hence the capabilities, of neuromotor prostheses of the future will raise new questions about who may properly benefit from them and in what ways (therapeutic, financial, perhaps even psychosocial).

In fact, Stephen Scott, also in that issue, suggests that through information-feedback circuits that already exist in the brain, the use of these prostheses may subtly modify the way the brain signals themselves are organized so that brain and man-made devices meld together increasingly well—a hopeful prospect for people with paralysis.<sup>8</sup>

Other technological advances, in the area of brain imaging, are raising concerns about “incidental findings,” unexpected signs of a possible disease that are discovered in the course of research on an unrelated topic. Reports of incidental findings are increasing. Writing in *Science*, a working group of about 50 experts from the fields of medical imaging, biomedical ethics, and law considered the question of whether researchers have an obligation to disclose such incidental findings to their study participants, and, if so, under what circumstances.<sup>9</sup>

The answers are far from obvious. Some of the illnesses that might be detected are very serious, yet the rate of false positives in this setting may be high, and in the end a firm result could come only from a second scan, to be read this time by a diag-



### Brain activity in a vegetative state

*A patient in a persistent vegetative state showed activity in the same brain areas as healthy volunteers in response to spoken commands to visualize herself playing tennis or moving through her house.*

nostic radiologist. If incidental findings show up on a research scan, does the research subject have a right to know about them, a right *not* to know, or both?

The working group urges all researchers who use brain imaging to decide in advance how incidental findings will be handled. This protocol should be stated clearly as a step in the informed-consent process, they say. Future research that focuses on incidental findings may, of course, lead to new recommendations, but ensuring scientific integrity and engendering public trust will remain the guiding principles.

### Nuances of Nonconscious States

Research in 2006 brought attention to unusual patients with severe brain injuries. In the *Journal of Clinical Investigation*, Henning Voss, Nicholas Schiff, and fellow researchers from New York, New Jersey, and New Zealand described the spontaneous rehabilitation of a man who had lain for 19 years in a minimally

*These feats are particularly impressive because they indicate, in a very concise manner, brain activity underlying so many aspects of what we think of as consciousness.*

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conscious state, unable to move or speak as the result of a car accident.<sup>10</sup> His condition had shown gradual improvement over the years; even so, his recovery of consciousness, fluent speech, cognition, and movement in three of his four limbs was unprecedented.

The researchers used a noninvasive imaging technique, magnetic resonance diffusion tensor imaging, to examine his brain. They found evidence of the regrowth of axons, which would enable new connections to form within the brain.

A second patient described in the paper, who (also as the result of a car accident) had spent more than a year in a persistent vegetative state and another four years in a minimally conscious state, has shown no comparable clinical improvement or axonal regrowth, but may yet do so. The authors call for more imaging studies using diffusion tensor imaging and also positron-emission tomography, beginning shortly after brain injury, in order to reveal more about the hopeful phenomenon of long-term rewiring in the brain.

An encouraging observation emerged as well about brain activity in a patient in a persistent vegetative state (PVS), from research in *Science* led by Adrian Owen.<sup>11</sup> After a car accident and five months in a persistent vegetative state, a young woman who appeared unresponsive underwent an fMRI scan of her brain that demonstrated clear evidence she could carry out several complicated cognitive tasks in a normal fashion.

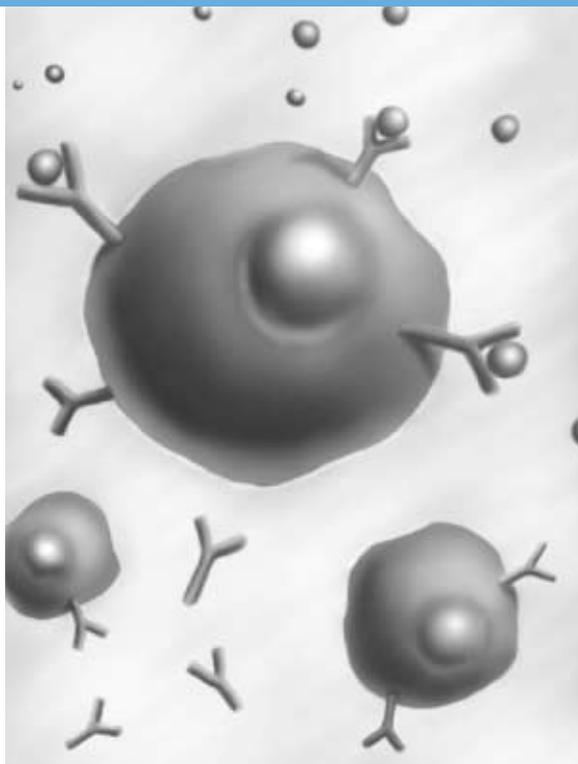
In response to spoken sentences, even those containing ambiguous-sounding words (“The *creak* came from a *beam* in the *ceiling*”), the language areas of her brain displayed activity equivalent to that of healthy volunteers. In addition, she showed normal brain activity in response to a spoken command to visualize herself playing tennis or walking through the rooms of her home.

These feats are particularly impressive because they indicate, in a very concise manner, brain activity underlying so many aspects of what we think of as consciousness: intention, aware-

ness of one's body, visual tracking of an (imagined) moving object, and the recollection of (imagined) familiar surroundings. Some neuroscientists had hypothesized previously about "islands" of preserved function in patients in a persistent vegetative state that might be undetectable by standard clinical methods. The mental agility of this immobile patient seems to confirm that such "islands" can occur as hypothesized and generates hope of uncovering some kind of window into the recesses of nonconscious states.

Because only a minute number of patients have been found to improve, questions arise about whether costly experimental interventions (such as deep brain stimulation or transcranial magnetic stimulation) to try to stimulate recovery of some communication functions should be used in all patients. Current research aimed at determining whether these interventions will be effective, and under what circumstances, may help to identify patients most likely to benefit.

# NEUROIMMUNOLOGY



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The human immune system often has a troubled relationship with the brain; the brain is an “immune privileged” area, where only one type of immune cell, called microglia, reside. Invading bacteria, viruses, and toxins can enter the brain by breaching the blood-brain barrier, the tightly packed layer of cells in blood vessel walls that governs the transfer of substances from blood to the brain. When this occurs, immune cells then rush into the brain to fight the invaders off.

Sometimes, however, immune cells mistake normal brain tissues as invaders and attack them. This occurs in multiple sclerosis, for instance, in which immune cells go overboard and attack the essential myelin insulation surrounding axons in the brain and central nervous system. The immune system also launches an attack against the amyloid proteins that build up in the brains of patients with Alzheimer’s disease; this attack is so aggressive that it provokes inflammation that damages neurons. A similar process may occur in Parkinson’s disease (see Movement Disorders, page 22).

The most significant advances in neuroimmunology in 2006 identified how certain immune cells become transformed to attack myelin in multiple sclerosis. Other research investigated how the immune system might serve to prevent or even reverse the degeneration of Alzheimer’s disease.

## **Multiple Sclerosis**

In multiple sclerosis, the gaps that develop in the myelin covering of nerve cell axons after repeated immune system attacks disrupt neural signaling. This disruption produces an array of symptoms. Until recently, scientists assumed that such myelin attacks were waged by faulty immune helper T cells (called  $T_H1$  cells), which ordinarily alert the immune system to the presence of bacteria or viruses within a cell. However, researchers discovered in 2005 that another helper T cell,  $T_H17$ , plays a crucial role in initiating an autoimmune attack on myelin. The  $T_H17$  cells are produced when immature T cells are exposed to the combination of two other molecules, according to a *Nature* study by researchers at Harvard Medical School in Boston, led by Estelle

Betelli.<sup>1</sup> One of these molecules is a signaling protein known as transforming growth factor-beta (TGF-beta). The other is an inflammation-promoting immune molecule called interleukin-6 (IL-6), which is released by T cells. Mice deficient in IL-6 had no T<sub>H</sub>17 cells and did not develop a mouse version of multiple sclerosis.

Moreover, Yoichiro Iwakura and Harumichi Ishigame found that a molecule called interleukin-23 (IL-23), a growth factor, transforms immature T cells into T<sub>H</sub>17 cells.<sup>2</sup> Their work, published in the *Journal of Clinical Investigation*, revealed that by blocking IL-23, they could significantly suppress the development of animal versions of multiple sclerosis and another autoimmune disease called inflammatory bowel disease. Taken together, these two studies suggest that therapies that block the transformation of immune T cells into T<sub>H</sub>17 cells might be effectively used in at least some autoimmune disease, including multiple sclerosis.

### **Target of an Autoimmune Attack**

In another inflammatory disease called neuromyelitis optica, the immune system attacks the myelin around the optic nerve, producing partial or total blindness. Although neuromyelitis optica is sometimes mistaken for an early manifestation of multiple sclerosis, scientists recently discovered that an antibody known as NMO-IgG, which mistakenly attacks the myelin in neuromyelitis optica, does not exist in patients with multiple sclerosis. This finding suggests that neuromyelitis optica is a distinct disease.

Research also suggests a role for NMO-IgG in transverse myelitis, a disease in which the immune system attacks the myelin around axons in the spinal cord, causing movement problems or paralysis. Brian Weinshenker and colleagues at the Mayo Clinic reported in *Annals of Neurology* that about 40 percent of patients with extensive transverse myelitis test positive for NMO-IgG, and more than half of those who test positive experience a relapse within one year.<sup>3</sup> Those without the antibody in their blood do not experience relapse.

Before this discovery, physicians could not identify which of these patients, including those with transverse myelitis, were at risk for a recurrent autoimmune attack on the spinal cord. Now,

*A runaway immune response in the brain can cause multiple sclerosis, lupus, and other diseases—but how does the immune system get out of control?*

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by testing for this biomarker, they can identify those at risk for relapse and consider starting immunosuppressive treatments.

But what does the NMO-IgG autoimmune antibody attack? Researchers at the Mayo Clinic led by Vanda Lennon discovered in 2006 that NMO-IgG mistakenly targets aquaporin-4, a recently discovered protein in the central nervous system that enables water to move in and out of cells.<sup>4</sup> Aquaporin-4 is produced in the brain primarily by star-shaped cells called astrocytes, which bolster the blood-brain barrier, dispose of noxious substances in the blood, and prevent them from passing into the brain.

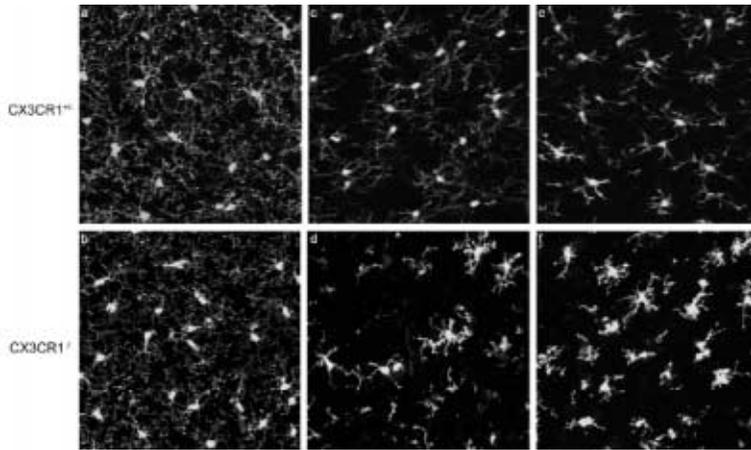
High levels of aquaporin-4 are found in the optic nerve, spinal cord, and certain brain stem areas—targets attacked by the immune system of patients with neuromyelitis optica. This suggests that NMO-IgG might leak from blood vessels at those locations, find aquaporin-4, and attack it. In any case, the finding that NMO-IgG is a reliable marker for the disease represents a major advance in diagnosis of neuromyelitis optica.

### **Controlling the Immune Response**

A runaway immune response in the brain can cause multiple sclerosis, lupus, and other diseases—but how does the immune system get out of control?

Chemokines send signals among cells and regulate the deployment of immune cells known as leukocytes. A team led by Richard M. Ransohoff reported in *Nature Neuroscience* that fractalkines, an unusual variant of chemokines, are essential for keeping immune reactions in the brain under control.<sup>5</sup> By releasing fractalkines, immune cells in the brain (the microglia) quell the tendency of other cells involved in an immune response to overreact.

Ransohoff found that mice lacking the gene for fractalkines appear normal but suffered much greater damage to their neurons during vigorous inflammatory reactions in mouse models of human diseases including Parkinson's disease and amyotrophic lateral sclerosis (Lou Gehrig's disease).



### Immune system control problems

*Mice lacking the gene for the fractalkine receptor protein, bottom, a protein found on brain inflammatory cells, show increased microglia activity over time (from left to right), causing greater neuron damage during mouse models of human diseases.*

## The Immune System and Alzheimer's

The immune system identifies the beta-amyloid particles that accumulate in the brains of people with Alzheimer's disease as foreign invaders that must be destroyed. The result is inflammation, which certainly aggravates the disease and may even cause it. A clinical trial of a therapeutic vaccine to deplete those plaques had to be stopped in 2002 because the immune reaction caused severe brain inflammation in some participants.

But the immune T cells that caused that inflammation still might be effectively and safely recruited as allies in a fight against those plaques, according to Michal Schwartz and colleagues at the Weizmann Institute of Science in Israel. In a paper published in *Proceedings of the National Academy of Sciences*, the researchers described how they therapeutically immunized mice bred to develop amyloid plaques by giving them glatiramer acetate (GA), an immune system modulator (trade name "Copaxone") that has been used to treat multiple sclerosis. The therapy, which stimulates T cells, reduced the plaque burden in the mice and promoted the growth of cells in the hippocampus, resulting in improved memory and learning.<sup>6</sup>

The scientists believe the therapy achieved this effect by stimulating microglial cells to express a hormone called insulin-like growth factor-1 (IGF-1) instead of the destructive cytokine called tumor necrosis factor-alpha (TNF-alpha), which triggers inflammation. By fine-tuning the immune response in this way, the authors believe, such therapies could stimulate an attack against beta-amyloid in the brain without triggering destructive inflammation.

Schwartz also demonstrated that when immune T cells are injected into the brains of mice, they contribute to the birth of neurons in certain areas, including the hippocampus, which is devastated by Alzheimer's disease. She and her group compared the brains of two groups of mice in a stimulating environment full of toys and novel objects: normal mice and mice with severe combined immune deficiency (SCID), which left them with virtually no T cells. While the normal mice displayed vigorous neurogenesis in the hippocampus, where short-term memories are generated, the SCID mice that lacked T cells displayed almost none.

A different approach to Alzheimer's that involves suppressing inflammation also showed promise in 2006. Researchers led by Edward Tobinick at the University of California, Los Angeles, conducted a six-month pilot study in which they administered etanercept, a therapy that counters TNF-alpha and is effective at suppressing inflammation in arthritis, to 15 patients with moderate to severe Alzheimer's.<sup>7</sup>

The weekly injections significantly improved the mental function of the participants. The study bolsters the theory that inflammation in itself is a major contributor to the dementia of Alzheimer's, and that suppressing it would help slow or even prevent mental decline.

Researchers at Case Western Reserve University, however, challenged the widespread hypothesis that the amyloid plaques

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*A group of researchers at Case Western Reserve University believes that attempting to cure Alzheimer's by eliminating plaques from the brain is fundamentally misguided.*

characteristic of Alzheimer's and the inflammation they trigger are the cause of the disease. Instead, they argue that symptoms result from oxidative stress, the increased production of oxidants, which they believe destroys neurons. In a report in *Current Alzheimer Research*, Hyoung-gon Lee, Mark Smith, George Perry, and colleagues argue that the plaques represent the brain's attempt to alleviate oxidative stress.<sup>8</sup> They believe that attempting to cure Alzheimer's by eliminating plaques from the brain is fundamentally misguided. A more effective approach, they say, would involve finding the causes of oxidative stress and minimizing them.

Meanwhile, Northwestern University Medical School researchers led by Abdelhak Belmadani discovered that chemokines, in addition to sending signals that regulate leukocytes, regulate the migration of neural progenitor cells to any site of inflammation in the brain, including the widespread inflammation caused by Alzheimer's. When inflammation injures nerve cells, astrocytes activate chemokines, which then direct adult neural progenitor cells to the site of inflammatory injury.

This finding could point the way to drugs that might contribute to the recovery of the brain after injury by encouraging this migration of neural progenitor cells to the site of injury, where they could develop into new neurons, the Northwestern researchers write in the *Journal of Neuroscience*.<sup>9</sup> This could conceivably help rebuild a hippocampus that had been damaged by Alzheimer's.

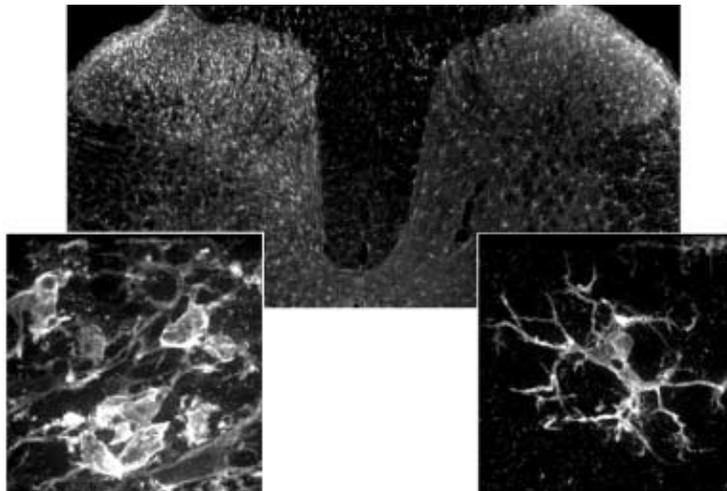
## **Neuropathic Pain**

Other research has implicated microglia in neuropathic pain, a chronic and frequently excruciating condition in which pain persists long after the injury, infection, or toxin that triggered it has cleared (also discussed in the Pain section, page 50).

Neuropathic pain may result after injury to "peripheral" nerves (those outside the brain and spinal cord). When pain does occur, microglial cells, the only immune cells that reside in the brain and spinal cord, are activated. They release brain-derived neurotrophic factor, which intensifies pain signals between microglia and neurons, according to researchers at the University of Toronto led by Michael Salter.

This process disrupts the normal suppression of pain, making neurons hypersensitive even in the absence of painful stimuli. The researchers reported their findings in the *European Journal of Physiology*.<sup>10</sup> The research suggests the signaling components of microglial cells may be promising therapeutic targets for reducing chronic peripheral nerve pain.

Elsewhere, researchers at Columbia University Medical Center applied for a patent to develop drugs that would block chronic pain by turning off an enzyme known as protein kinase G (PKG). They reported in the journal *Neuroscience* that the activity of PKG contributes to neuronal hyperexcitability, which



### Microglia mediate pain

*After injury to peripheral nerves, microglia in the dorsal horn of the spinal cord become activated, making neurons hypersensitive and creating a sensation of pain even when no painful stimulus is present.*

results in the production of persistent pain signals.<sup>11</sup> They found that turning off the PKG switch stopped the pain, which makes the enzyme an ideal target for drugs.

### Plasticity

Youthful brains rewire themselves vigorously in response to injury. Although such rewiring, called plasticity, becomes progressively slower with age, researchers at Harvard Medical

School have found that an immune system protein known as paired-immunoglobulin-like receptor-B (PirB) may gradually inhibit plasticity over time, stabilizing brain connections. A team led by Josh Syken reported these findings in *Science*.<sup>12</sup>

They found that mice deprived of PirB exhibited greater rewiring ability throughout life. That suggests that finding a way to reduce PirB might help to re-establish connections among neurons damaged by spinal cord injury, stroke, or other trauma.

### ***Depression Can Lead to Inflammation***

Researchers at the Emory University School of Medicine in Atlanta found that the immune systems of depressed men with early life stresses produce exaggerated inflammatory responses to stress that may contribute to poor health outcomes from inflammatory diseases.

Exposure to stress generally results in an increase in the production of interleukin-6 (IL-6), which promotes inflammation. The researchers, led by Drs. Andrew H. Miller and Christine Heim, tested 28 men, half of them diagnosed with major depression and early life stress. After they were subjected to tasks such as solving math problems and public speaking, which increase stress, blood samples were tested for the presence of IL-6.

Although IL-6 increased in all participants, levels rose almost twice as high in the depressed group, the researchers reported in the *American Journal of Psychiatry*.<sup>13</sup> The study provides preliminary indication of a link between major depression, early life stress, and health outcomes.

# PAIN



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Pain is a major problem for physicians and the public alike, resulting in nearly \$100 billion in lost productivity and health-care costs each year, according to the nonprofit Partners Against Pain. In 2006 general pain researchers around the globe advanced understanding of what underlies acute and chronic pain, as well as ways to alleviate it.

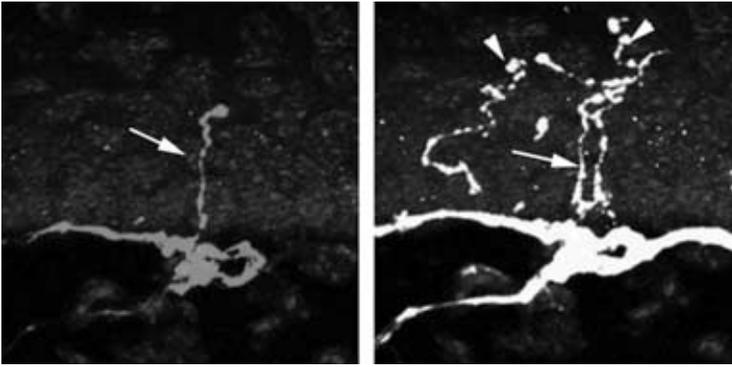
One study identified a “master switch” for the development of neuropathic pain, a chronic form of pain quite different from the acute pain of an injury. Another found that simply anticipating pain may be worse than actually experiencing it. Researchers looking for pest controls stumbled onto an enzyme blocker that may provide relief from inflammatory pain while decreasing the risk of heart attack associated with drugs such as rofecoxib (Vioxx). Canadian scientists found that mice display empathy and become sensitive to pain while watching another mouse experience pain. And researchers found that the type of placebo and the context in which it is given may enhance the placebo effect on pain perception.

### ***Master Switch Identified for Chronic Pain***

Neuropathic pain, from injury to “peripheral” nerves outside the brain and spinal cord, is characterized by a chronic shooting or burning sensation. It responds poorly to treatment with opioid drugs, which are the strongest painkillers and include such drugs as morphine, codeine, and oxycodone (brand name Oxycontin).

In the journal *Neuron*, researchers at Harvard Medical School reported finding a “master switch” for the development of neuropathic pain.<sup>1</sup> This switch, the Runx1 gene, is expressed only in sensory nerve cells called nociceptive cells, which are involved in sensing pain. These cells translate painful stimuli into nerve signals via ion channels, special pores in the nerve cell membrane.

The researchers, led by Qiufu Ma, exposed “knockout” mice (in which the Runx1 gene was removed) to thermal, mechanical, inflammatory, and neuropathic stimuli and measured their reaction to pain by how long they either lifted or licked their paw in response.



### Limiting pain

*A gene called Runx1 is active in pain receptors for thermal and inflammatory pain, indicated by arrows, and neuropathic pain, indicated by the arrowheads. Mice lacking the Runx1 gene did not react to these types of pain.*

While the Runx1-deficient mice responded to the mechanical pain stimulus, they showed no reaction to the painful thermal, neuropathic, or inflammatory stimuli. The development of pain-receptor cells was impaired and the ion channels known to be involved in sensing thermal and neuropathic pain were nonexistent.

The findings could have important implications for developing new, more effective treatment strategies for neuropathic pain, possibly by turning off the expression of the Runx1 gene in patients suffering from chronic pain, the researchers said.

### Anticipating Pain May Be as Bad as Pain Itself

Waiting for a shot in the doctor's office or looking ahead to a painful medical procedure causes some people to think, "Just get it over with. I don't care how much it hurts!" Scientists may now know why: for some of us, anticipating pain may be as bad as actually experiencing it.

Using brain scans to study the biology of dread, a team of researchers at Emory University School of Medicine found that almost one third of study participants who volunteered to receive an electric shock chose to receive a stronger jolt in exchange for getting the ordeal over with rather than waiting for a weaker one. Volunteers were placed inside a magnetic resonance imaging machine and given a series of 96 electric shocks,

*The more a person dreads an event, the more attention the brain's pain-sensing centers pay to the amount of time until the event occurs.*

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of varying intensities, to the foot. Most volunteers chose to receive a stronger electric shock if the waiting time before the shock was shorter.

The findings, reported by Gregory Berns and colleagues in *Science*, indicate that a majority of individuals in the study dreaded waiting for a shock.<sup>2</sup> Those who could not tolerate a delay and chose an immediate and more painful jolt were considered “extreme dreaders,” while “mild dreaders” could endure a delay for a milder shock.

The magnetic resonance scans showed that parts of the brain’s “pain matrix,” a network of brain regions that respond to noxious stimuli including pain, became active even before the study participants were given the shocks. Regions of the brain involving fear and anxiety showed no response prior to the jolt that distinguished the mild from the extreme dreaders. The results demonstrate that the more a person dreads an event, the more attention the brain’s pain-sensing centers pay to the amount of time until the event occurs.

It is not yet clear how these preferences relate to how people deal with events that are known to be unpleasant, such as going to the doctor for a painful procedure, but the neurobiological underpinnings of dread may hold some clues for better pain management in the future.

## ***Pain Control from Pest Control***

After the earlier withdrawal of the popular pain reliever Vioxx (rofecoxib) from the market because of safety concerns, researchers at the University of California, Davis, may have stumbled upon a safer way to deliver needed pain relief for people suffering from arthritis or other inflammatory diseases.

The researchers started out with an unrelated goal: to find biological pest controls that would regulate the development of

insect larvae. However, in the course of their study they discovered a new human enzyme that indirectly blocks the production of COX2 proteins, which are involved in pain and inflammation.

Using the two therapies in combination may lead to relief of inflammatory pain and decrease the side effects of drugs used to alleviate that pain. In testing on rodents, the researchers found that the enzyme blocker was as potent as low doses of rofecoxib and another COX2 inhibitor, celecoxib (Celebrex), but without producing changes in blood chemistry that were linked to serious cardiovascular complications, including heart attacks, in an earlier study—the finding that led to Vioxx’s removal from the market. The new study was published in *Proceedings of the National Academy of Sciences*.<sup>3</sup>

A combination of the two types of COX2 blockers could dramatically reduce the concentrations of Cox-2 inhibitor needed to effectively treat inflammation, the researchers said. This combination apparently changes blood chemistry in a way that reduces the tendency for blood clots to develop, a key feature of heart attacks. Combination therapy such as this may help solve the dilemma of whether to use powerful Cox-2 inhibitors to treat inflammatory pain.

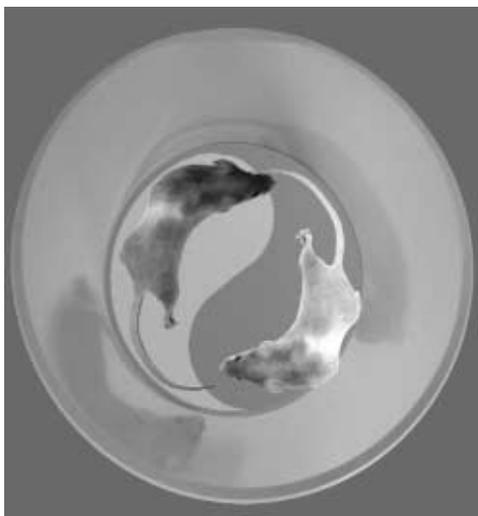
### **“Emotional Contagion” of Pain**

Previous pain research has shown that early-life experiences and certain social factors can make chronic pain worse. For instance, German scientists found that social factors can alter brain function in a way that worsens pain sensations.<sup>4</sup> Another study showed that pain experienced early in life can affect how pain is experienced in adulthood.<sup>5</sup> A new study, reported in *Science*, by Jeffrey Mogil and colleagues shows that a mouse’s response to pain is intensified in the presence of another mouse in pain, suggesting that empathy plays a role in pain.<sup>6</sup>

Using an acetic acid writhing test, which simulates a mild stomachache, the researchers, at McGill University’s Pain Genetics Laboratory, determined that mice that were familiar with one another showed a subclass of empathy called “emotional contagion,” in which one mouse recognizes and adapts to the emotional state of another. The researchers found that a

## Your pain and mine

*A mouse in pain felt it more intensely when in the presence of another mouse in pain, which suggests that empathy has an effect.*



mouse became more sensitive to acetic acid while watching another mouse experience a painful heat stimulus.

Mice rely on pheromones (chemical substances that transmit messages between members of the same species) to interact with one another. The investigators blocked the rodents' senses of smell, vision, and hearing and found they could still sense one another's pain, suggesting that some form of communication among them affected their response to pain.

Because social interaction plays an important role in chronic pain behavior, the McGill findings may be relevant to the study of pain in humans. The findings in the mouse model may be used to study the human brain mechanisms involved in pain, as well the role social factors play in pain management.

## **Type of Placebo Has an Effect**

More than 50 years ago, a Harvard anesthesiologist named Henry K. Beecher first described the role placebos play in medicine. The placebo effect is the phenomenon of a patient's symptoms being alleviated by an otherwise ineffective treatment because the individual expects or believes it to work.

In two studies, published in the *British Medical Journal* and the *Journal of Neuroscience*, a research team led by Ted Kaptchuk of Harvard Medical School's Osher Institute demonstrated that the

*The placebo effect can be modulated by the type of placebo given, as well as by the context in which it is delivered.*

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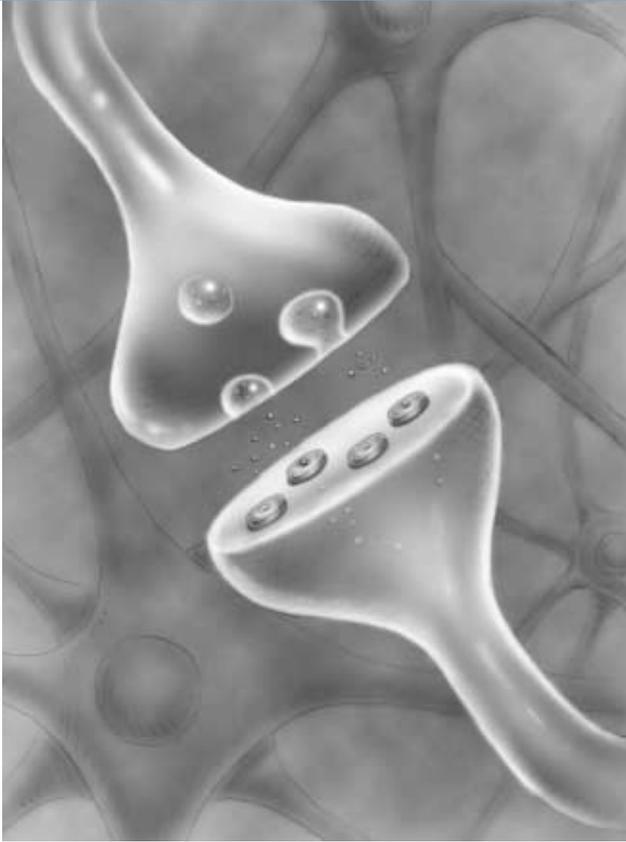
placebo effect can be modulated by the type of placebo given, as well as by the context in which it is delivered.<sup>7,8</sup>

In the first study, Kaptchuk's group gave sham acupuncture to 135 patients suffering from severe arm pain, while another 135 received an inert pill, to determine which placebo treatment had a greater effect. Neither proved to have a superior effect. In a later study, half of each group remained on their original placebo treatment while the other half received active treatment.

The patients receiving the sham acupuncture reported greater reduction in pain than those taking the inert pills. Kaptchuk says the findings suggest that the "ritual" of receiving treatment with a device such as sham acupuncture may enhance the placebo effect more so than an inert pill, a possibility he and his colleagues continue to study.

The researchers also used functional magnetic resonance imaging to determine the brain networks activated by sham acupuncture during the round of testing that included some patients receiving an active treatment. Building on previous studies that discovered pathways involving the prefrontal cortex, striatum, and brain stem for processing placebos, the researchers found that specific areas of the brain are particularly associated with the placebo effect. One of them is the anterior insular cortex, which activates bodily feelings, including pain. These studies add to the growing body of evidence that the so-called placebo effect has a basis in changed brain functions.

# PSYCHIATRIC, BEHAVIORAL, AND ADDICTIVE DISORDERS



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As was the case in 2005, mental health research in 2006 continued its concentration on the role of genes in mental disorders and the effects of the interaction of those genes with environmental factors. However, 2006 brought with it a new focus on clinical and genetic investigations of treatments for those disorders.

Research in schizophrenia examined the clinical effectiveness of newer antipsychotic drugs in comparison with their predecessors. Genetic studies in depression focused on possible predictors of antidepressant treatment outcomes, evidence of whether antidepressant treatment is linked to suicide, and how treatment of depressed mothers affects the likelihood of depressive symptoms and diagnoses in their children.

## Schizophrenia

Antipsychotic medications have long been the primary treatment for patients with schizophrenia. Unfortunately, many traditional drugs come with a host of disagreeable side effects related to the inhibition of the neurotransmitter dopamine. As a result many psychiatrists are now prescribing second-generation or “atypical” antipsychotics that are less likely to block dopamine transmission in brain areas not directly affected by the disorder. But is this new class of therapeutic agents more effective and tolerated better by patients than the first-generation therapies?

Most are not, according to work in 2005 and 2006 by Jeffrey Lieberman and colleagues. Research published in 2005 revealed no difference in effectiveness between the first- and second-generation antipsychotics.<sup>1</sup> In terms of tolerability, olanzapine, a second-generation drug, showed a slightly lesser rate of discontinuation by patients of their medication compared to other drugs, but it was associated with unpleasant weight gain and metabolic side effects.

Lieberman’s group continued their work in 2006, publishing two papers in the *American Journal of Psychiatry* that examined antipsychotic treatment in more detail. The group found that chronic schizophrenic patients were more likely to continue treatment if they were taking olanzapine and risperidone rather than other atypical antipsychotics.<sup>2</sup>



### Differences in antipsychotic drugs

*Researcher Jeffrey Lieberman has compared the effectiveness of first- and second- generation antipsychotics and has found that the newer generation actually is less effective on the whole.*

Correspondingly, in patients who did not respond to previous atypical antipsychotic medication at all, the investigators looked at the effectiveness of clozapine, a “last-resort” medication with strong side effects for treatment-resistant patients. They found that these patients responded better to clozapine than to a second atypical antipsychotic.<sup>3</sup>

In an independent study across the Atlantic, Peter Jones at Cambridge and his team of researchers also studied the effectiveness of second-generation antipsychotic medications in treating chronic schizophrenia. Participants were randomly prescribed either a first- or a second-generation antipsychotic drug and were evaluated for one year by a clinician who did not know which medication they had been assigned.

Symptoms, adverse effects, and quality of life were measured and compared. Jones’s team expected to find that the atypical drugs were more effective than their predecessors but, in fact, they found the opposite to be true. Patients responded better and scored higher on quality-of-life scales when taking the first-generation drugs.<sup>4</sup>

As might be expected, this finding, coupled with Lieberman’s research, has caused some consternation among psychiatrists. Together, these results suggest that atypical antipsychotic drugs

*Research on the elusive causes of schizophrenia continues to focus on the role of dopaminergic neurons.*

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generally should be tried primarily if patients are resistant to first-generation antipsychotic medications.

Research on the elusive causes of schizophrenia continues to focus on the role of dopaminergic neurons. Early research implicated excessive dopamine transmission in the disorder's behavioral symptoms. But Michael O'Donovan, Michael Owen, and their collaborators studied the abnormal function of brain cells called glia as another possible precursor to the disorder, based on prior postmortem and neuroimaging evidence of both structural and volume differences in brain white matter (the neural connections) between patients with schizophrenia and healthy controls. Glial cells interact with neurons to produce myelin, a fatty insulator that helps facilitate transmission of electrical signals from one brain cell to another.

The group's findings, published in *Proceedings of the National Academy of Sciences*, indicate that variation in a gene called OLIG2, which regulates the creation of myelin, makes carriers vulnerable to schizophrenia. This finding suggests that further research into the genes governing glial function on the production of myelin may provide important insights into the complex processes involved in schizophrenia.<sup>5</sup>

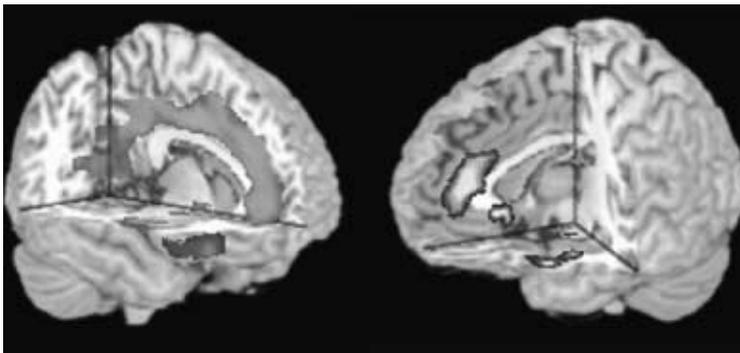
## **Violence and Aggression**

Researchers have attempted to pinpoint underlying causes of violence and aggression in humans for hundreds of years. Though the socio-environmental side of the equation has been explored in depth, underlying genetic components have been more difficult and controversial to study.

To date, the most substantiated genetic link associated with violent behavior involves monoamine oxidase A (MAOA), an enzyme directly involved in the metabolic breakdown of the neurotransmitter serotonin. In a paper published in *Proceedings*

of the *National Academy of Sciences*, Andreas Meyer-Lindenberg and colleagues reported the results of a study that used voxel-based morphometry, a computer-based neuroanatomical method that measures differences in concentrations of brain tissue, and functional magnetic resonance imaging to study the role of MAOA. They found that people with no history of a violent psychiatric disorder, but who had a gene variation that lowered MAOA enzyme expression, showed significant structural and functional brain differences compared to people with higher MAOA expression.

People with reduced MAOA expression showed not only reduced volume of gray matter in the cingulate gyrus, amygdala, and anterior cingulate cortex but also increased activation of the amygdala and limbic regions—areas implicated in emotional processing—when asked to distinguish angry faces from fearful ones.



### Gene linked to violence

*Group data from two types of magnetic resonance scans show that in people with a gene variation linked to aggression, the volume and activity of a region called the anterior cingulate cortex, shown in dark gray, are reduced. The region helps regulate emotional and aggressive responses.*

The study also revealed a sex component: male participants exhibited enhanced activity of the amygdala and hippocampus, compared with females, during an emotional memory task. The researchers note that although multiple factors contribute to violent behavior, these findings suggest a possible biological predisposition for impulsive violence, especially in males with this particular gene variation.<sup>6</sup>

## Anxiety Disorders

Genes were also the focus of research on anxiety-related disorders in 2006. Using mouse models, Carrolee Barlow's group at the Salk Institute identified 17 genes with expression patterns associated with typical anxiety disorder symptoms. Their paper, published in *Nature*, also discusses two genes involved with oxidative stress metabolism, the increased production of oxidants that result in the degeneration of neurons, as potential causes for anxiety-related disorders. By transferring these genes into cells through viruses, Barlow's team found that when the genes were overexpressed in mice, anxiety-like behavior increased.<sup>7</sup>

In a similar vein, a group led by David Goldman examined genes that are associated with one specific anxiety disorder: obsessive compulsive disorder, or OCD. His group found that HTT, a serotonin transporter gene, is implicated in OCD. In a paper published in the *American Journal of Human Genetics*, they discuss the finding that HTTLPR, previously thought to have only two genetic variants, actually has three. Multiple genotyping methods revealed a previously unknown variation of this gene, which could lead to new understanding of the neurobiology of OCD.<sup>8</sup> The bases for these alterations of behavior have been difficult to discern. Perhaps these newer genetic approaches will provide more definitive information.

## Depression

There continues to be interest in the use of deep brain stimulation for the treatment of those with depression resistant to the usual medications. Further studies by Helen Mayberg and colleagues at Emory University may help reveal whether this treatment is effective in a broader range of patients.<sup>9</sup>

Among other approaches were studies of genetic factors that may influence the response to more conventional antidepressant treatments. Researchers led by Francis McMahon examined the genetic basis of individual variations in antidepressant treatment outcomes. By studying the DNA of 1,953 patients with major depressive disorder being treated with citalopram, a common antidepressant, they demonstrated a significant association

*When mothers were successfully treated with medication for depression over three months, their children showed a reduction in depressive and other symptoms and diagnoses.*

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between favorable treatment outcome and the A variant of a gene responsible for serotonin reception, HTR2A. The results of the study are reported in the *American Journal of Human Genetics*.<sup>10</sup>

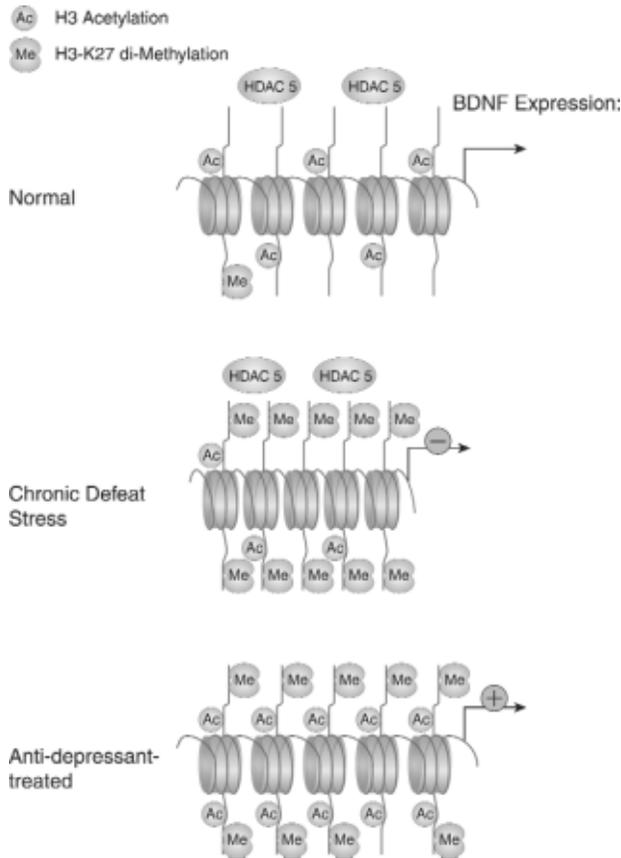
Furthermore, this A variation was found to occur six times more frequently in Caucasian patients than in African-American patients, who correspondingly showed poorer response to citalopram treatment. The findings provide a compelling case for the role of this gene in antidepressant action, and may help to explain racial differences in responses to antidepressant treatments.

Elsewhere, Myrna Weissman and colleagues illustrated an interesting phenomenon involving depression in children. It has long been known that children of depressed parents are at high risk for developing a depressive disorder of their own. Weissman's group reported in the *Journal of the American Medical Association* that when mothers were successfully treated with medication for depression over three months, their children showed a reduction in depressive and other symptoms and diagnoses.

Conversely, children of mothers who remained depressed suffered from an increased rate of symptoms. This suggests that environmental effects can also affect the psychopathology of this high-risk group of children.<sup>11</sup>

## **Teenage Suicide**

Researchers led by Mark Olfson looked at a different facet of antidepressant treatment: its relationship to suicide attempts and deaths in adults and children. The results of their matched case-control study, published in the *Archives of General Psychiatry*, revealed that although antidepressant treatment was not associated with either suicide attempts or deaths in adults, it was significantly associated with both suicide attempts and deaths in children and adolescents. This finding suggests at a minimum that drug treatment in younger patients needs to be closely supervised by clinicians, and parents.<sup>12</sup>



### Depression treatment

*Stress from chronic social defeat causes a drop in a protein called brain-derived neurotrophic factor, center, research in mice has shown. Treatment with an antidepressant, bottom, brought BDNF levels back up.*

The neurobiology of stress-induced depression was the focus of Eric Nestler's research group. In a study in *Nature Neuroscience*, mice were subjected to chronic social defeat stress, a frequent precursor to depressive disorders, followed by the chronic administration of imipramine, an antidepressant. Nestler's group found that this defeat stress generated a decrease in a protein called brain-derived neurotrophic factor (BDNF) in the hippocampus as well as increased modifications to specific proteins associated with gene transcription, called histone methylation.

The antidepressant agent reversed this effect, as did an infusion of BDNF itself. The findings suggest that histone methylation and the neurobiological processes related to it may provide a new area of therapeutic interest for depression treatment.<sup>13</sup>

Meanwhile, Michel Lazdunski and his collaborators identified a different area of interest for future antidepressant development. Writing in *Nature Neuroscience*, Lazdunski's group reported their discovery that a background potassium channel regulated by serotonin, TREK-1, was implicated in depression resistance in mice. Those without the TREK-1 channel showed a resistance to depression under stress, suggesting that this channel may be a viable target for new drug interventions for depression.<sup>14</sup>

## Cocaine Addiction

Does increased dopamine release underlie the craving for drugs? Researchers led by Nora Volkow delved deeper into why drug-related cues can produce persistent conditioned responses in former addicts and found that the answer may be yes.

Previous brain imaging studies have associated those responses with activation in specific limbic structures. Using positron-emission tomography, Volkow's group demonstrated a conditioned dopamine release in the dorsal striatum of former cocaine addicts when they were shown a cocaine-related video.

These results, published in the *Journal of Neuroscience*, suggest that therapies designed to restrain dopamine increases may assist in the treatment of addiction.<sup>15</sup>

Finally, functional brain imaging studies have demonstrated that several brain regions, including the prefrontal cortex and the amygdala, are activated during drug-associated cues. These areas are linked to another area of the brain, the ventral tegmental area, or VTA. Synaptic changes in the VTA may provide researchers clues into the neurobiological causes of drug addiction, withdrawal, and relapse.

Mu-Ming Poo and colleagues examined the dopaminergic neurons in the VTA of rats after cocaine withdrawal and reported their findings in *Nature Neuroscience*. They found heightened brain-derived neurotrophic factor (BDNF) in those cells of the rats. During withdrawal, the dopaminergic neurons in the VTA may be primed by this increased BDNF expression, starting a chain of events that could elicit a craving for the drug when a person is exposed to reminders of past drug use.<sup>16</sup>

# SENSE AND BODY FUNCTION



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Advanced technology has allowed scientists to peer deeper than ever before into the inner workings of the brain, expanding our understanding of the complex relationship between the brain, the senses, and body function. This vast area extends from specialized genomic tools to explore the mechanics of rapid-eye-movement sleep to studies of the influence of circadian clocks on feeding, as well as identifying a section of the brain devoted solely to face recognition. Other studies in 2006 revealed new information about hearing, smell, taste, and sight, answering old questions and raising new ones.

### ***Hearing: Regenerating Hair Cells in Mammals***

Sensorineural hearing loss, currently an irreversible condition, is the most common type of deafness in the United States. It is caused by damage to specialized inner-ear hair cells, from aging, exposure to loud noises, and side effects from certain medications. Scientists interested in developing new therapies for certain types of hearing loss got a boost in 2006 from research that suggests that these specialized hair cells, vital to hearing, may be able to regenerate.

Although damaged sensory cells in the inner ear, or cochlea, of birds and other lower vertebrates can regenerate, cells in cochlea in mammals, including humans, cannot. Hair cells have long been a target of research aimed at developing new treatments for sensorineural hearing loss. In a study reported in *Nature*, Neil Segil, Andy Groves, and colleagues at the House Ear Institute in Los Angeles discovered that a gene known as p27Kip1 prevents cell division in the inner ear.<sup>1</sup>

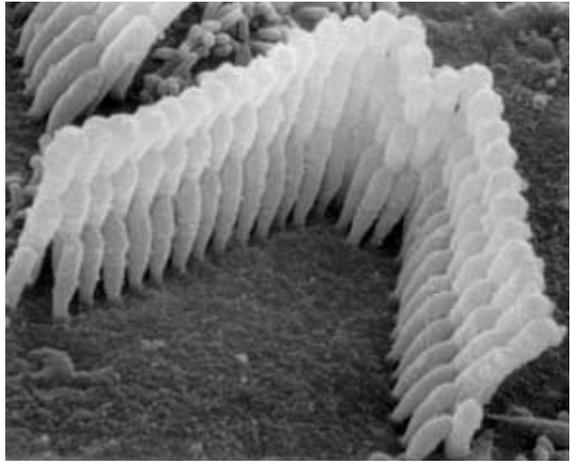
The researchers studied mouse sensory cells in culture. They found that this gene was switched off in newborn mice, allowing the supporting cells to proliferate and differentiate into hair cells. Studies of cultures from two-week-old mice, however,

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***The work holds promise for the development of new therapeutics to reverse deafness in humans.***

## Hear, hair

*An image of a hair cell from a high-power scanning electron microscope shows hair bundles projecting from the surface of the cell. Researchers have found in mice that silencing a gene allows hair cell growth that could restore hearing.*



revealed that this gene, p27 for short, was now switched on, halting cell division. However, cells from two-week-old mice genetically altered to lack the p27 gene were able to make hair cells, suggesting that by silencing the gene, researchers may be able to stimulate inner ear hair cell growth to restore hearing.

While this process has been shown only in mouse cultures, the work holds promise for the development of new therapeutics to reverse deafness in humans.

## Why Faces Are Familiar

A study published in *Science* adds weight to one side of a long-standing debate among neuroscientists about whether the brain is divided into specialized areas dedicated to performing a specific task.<sup>2</sup> In the study, scientists at Harvard Medical School and the University of Bremen in Germany have identified an area of the visual cortex in which almost all of the neurons are specialized for just one task: face perception.

Using functional magnetic resonance imaging, a team led by Margaret Livingstone identified three areas of the cortex in macaque monkeys believed to be important in face recognition. Monkeys were shown 96 images, including pictures of faces, bodies, fruits, gadgets, hands, and scrambled grid patterns. Scientists then recorded neuronal impulses from individual cells in the largest of these three brain regions. They found that almost all (97 percent) of visually responsive neurons were 50 times more likely

## *Humans may have specialized cells solely devoted to facial recognition.*

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to respond to faces than to the other visual stimuli. In fact, the only other images that sparked a response from these neurons were round objects similar to the shape of faces.

Strong physiological similarities between the macaque brain and the human brain suggest that humans may have the same specialized cells solely devoted to facial recognition. Using imaging to analyze the process of face detection could lead to newer methods for lie detection (see also Neuroethics, page 35).

## ***Pheromone Detection***

The brain systems of many animals allow for detection of pheromones, chemical signals that help animals attract mates. However, the human brain appears to lack this ability, a scientific mystery given recent findings that suggest that humans can respond to pheromones. One possibility is that the olfactory epithelium, which contains neurons that recognize ordinary odors, may also detect pheromones.

Scientists at the Fred Hutchinson Cancer Research Center in Seattle set out to explore the epithelium's potential role in pheromone detection in mice. In research reported in *Nature*, Stephen Liberles and Linda Buck identified a set of olfactory receptors in the mouse nose called trace amine-associated receptors, or TAARs.<sup>3</sup>

The receptors are different from those that sense odors, and earlier studies suggest that some are activated by compounds in pheromone-rich mouse urine. In their study, Liberles and Buck found that one of the compounds TAARs recognize, isoamylamine, is thought to act as a pheromone that accelerates puberty in female mice.

This, coupled with other findings, suggests that TAARs may provide an alternate pheromone-detection method. Because the genes that encode TAARs are also found in fish and humans, it is possible that humans use these receptors to detect pheromones.

## REM Sleep Circuitry

Scientists discovered rapid-eye-movement (REM) sleep, associated with dreaming, more than 50 years ago. But just how the brain switches from REM to non-REM sleep remains unknown.

Researchers from Harvard Medical School released findings in 2006 that suggest a new model for how the brain controls the switch into and out of REM sleep. The study, reported in *Nature* by Clifford Saper and colleagues, also examines how the dream states and loss of muscle tone seen during REM sleep are activated.<sup>4</sup>

Previous models stressed interactions between cholinergic neurons, which are active during REM sleep, and monoaminergic neurons, which are silent during REM sleep. However, the model the Harvard team developed, which the scientists call the “flip-flop switch,” found that deactivating these two types of neurons had little effect on REM sleep.

Rather, they found that a reciprocal interaction between neurons releases a chemical messenger called gamma-aminobutyric acid, which is widely distributed in the brain, binds to neurons, and reduces their activity.

Problems in regulating this interaction may explain a number of puzzling sleep disorders, such as REM behavior disorder, in which patients act out their dreams, and hypnagogic hallucinations, in which they have dreamlike hallucinations while still awake.

Attempts to develop sleep-inducing drugs have generally ignored the various stages of sleep. Understanding the regulation of these stages could lead to better treatments for sleep disorders.

## Circadian Clocks and Feeding

Scientists have long known that when animals are given access to food only during their normal sleep cycles, they will alter their sleep patterns and biological functions to be awake and active when food is available. Two independent studies published in 2006 by teams at Harvard Medical School and the University of Texas Southwestern Medical Center may explain what enables animals to make this switch.

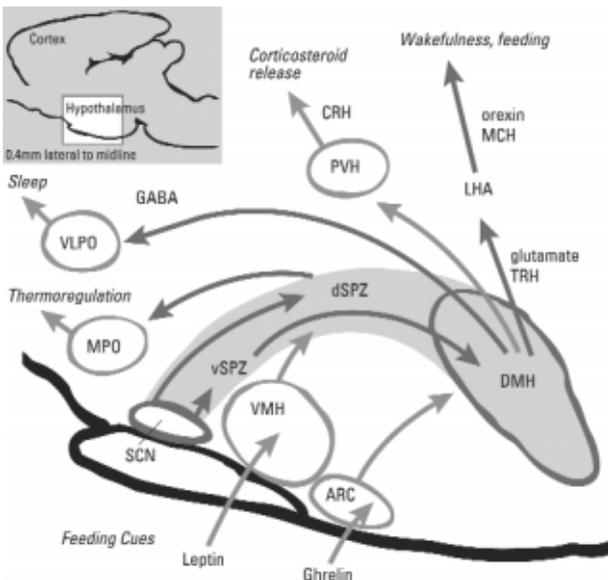
One team, led by Saper at Harvard, focused on a region of the brain called the dorsomedial nucleus of the hypothalamus, or

**Scientists found that the DMH can override the brain's biological clock and establish a new clock time to take advantage of food availability.**

DMH, which communicates with parts of the brain involved in feeding, energy consumption, the regulation of sleep and wakefulness, and body temperature, among other processes. The scientists, reporting in *Nature Neuroscience*, found that the DMH can override the brain's biological clock and establish a new clock time to take advantage of food availability.<sup>5</sup>

The second study, published by Masashi Yanagisawa and colleagues in *Proceedings of the National Academy of Sciences*, shows that the DMH neurons contain a normally nonfunctional clock that, when faced with restricted food availability, synchronizes itself to the time the food is available, allowing the DMH to establish its own circadian rhythms that override the brain's biological clock.<sup>6</sup>

The findings from both studies offer new targets for future research on circadian clocks and feeding, work that one day could have implications for treating obesity.



### Eating and sleeping to survive

The dorsomedial nucleus of the hypothalamus (DMH) coordinates cycles of sleep and wakefulness, feeding, and body temperature, among others. Research shows that this region can override the brain's clock, the suprachiasmatic nucleus (SCN), according to when food is available.

## Sour-Taste Receptor Identified

Humans savor foods with the aid of taste buds on the tongue that detect five specific tastes: bitter, sweet, salty, sour, and umami (the flavor of monosodium glutamate). Scientists have identified receptors that detect three of these: bitter, sweet, and umami.

Studies in 2006 by two independent research teams identified a protein that allows humans and some animals to sense sour tastes, including flavors that warn against eating spoiled or unripe food. The research, reported in *Nature* and *Proceedings of the National Academy of Sciences*, identified the protein as PKD2L1. It is present in some taste buds but absent in those that recognize sweet, bitter, and umami tastes.<sup>7,8</sup>

A group led by Charles Zuker at the University of California, San Diego, who reported the work in *Nature*, genetically engineered mice lacking PKD2L1. The animals responded to other tastes, but when given citric acid, vinegar, and other sour flavors, the mice did nothing.

Meanwhile, a team led by Duke University researcher Hiroaki Matsunami suggested in *Proceedings of the National Academy of Sciences* that the findings could lead to a better understanding of how the brain processes sensory information and could one day be used by the manufacturing industry to alter the taste of foods.

## Stem Cells and Vision

In vision research, findings point to embryonic stem cells as a possible treatment for age-related macular degeneration. The disease, the leading cause of blindness among people over 65, is caused by a deterioration of the retina and macula, which is located at the center of the retina and allows for detailed, central vision.

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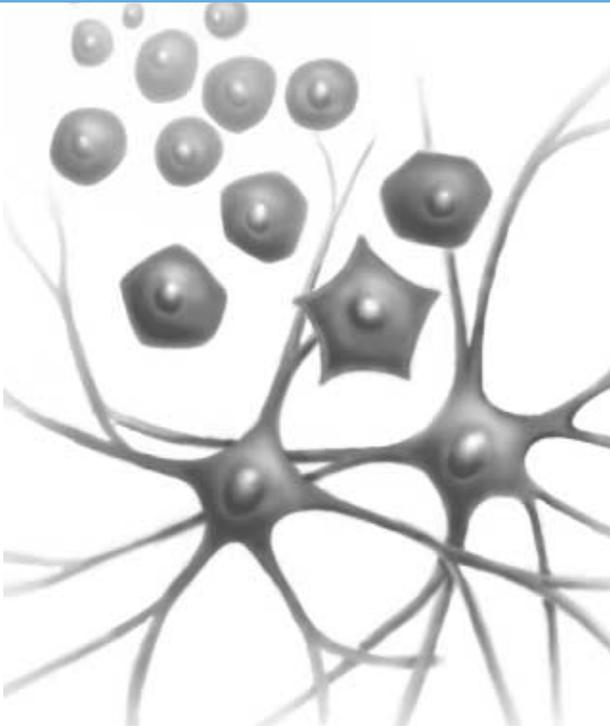
***The scientists examined the rats' vision and found that those that received the transformed stem cells had retained much of their sight, while the untreated rats were nearly blind.***

Retinal pigment epithelium cells, which line the base of the retina, can be damaged in some types of macular degeneration. In the study, reported in *Cloning and Stem Cells*, a team at Oregon Health and Science University led by Raymond Lund transformed embryonic stem cells into these retinal pigment epithelium cells, and then injected the cells into the eyes of rats with eye disease.<sup>9</sup> About six weeks later, the scientists examined the rats' vision and found that those that received the transformed stem cells had retained much of their sight, while the untreated rats were nearly blind.

In a similar study, researchers led by Robin Ali at University College London transplanted the cells that form the receiving cells of the retina, the photoreceptors.<sup>10</sup> Taken together, these studies indicate a possible application of stem cells and other primitive cells to the treatment of macular degeneration.

Although the findings are promising, the scientists cautioned that the rat eye disease is unlike macular degeneration in humans, and that more studies are needed to determine whether stem cells can be used to treat the human form of the disease.

# STEM CELLS AND NEUROGENESIS



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The birth of neurons, called neurogenesis, is known to continue throughout life in some areas of the brain. Research continues to show that the process is one of the brain's methods of self-repair that could be harnessed for therapeutic purposes; abnormal neurogenesis may contribute to some disorders and may provide new avenues for therapy. So too do the immature and versatile cells known as stem cells continue to show promise as treatments. Researchers made progress in 2006 in unraveling the pathways through which stem cells develop into neurons. But can stem cells take on specific jobs in the brain?

### **Neurogenesis in the Cortex**

Neurogenesis has been known since 1998 to occur in the hippocampus of the adult human brain. Less clear is whether new neurons are produced in other areas, and whether the brain's remarkable adaptability, or plasticity, results from the remodeling of existing cells or the production of new ones.

An innovative method for dating brain cells is the use of radio-carbon ( $^{14}\text{C}$ ), which was released in massive amounts during aboveground nuclear testing in the 1950s and has declined measurably ever since, taken up by the earth's atmosphere and into the DNA of plants, animals, and humans. In 2005 a team led by Jonas Frisen of the Karolinska Institute in Stockholm used  $^{14}\text{C}$  dating to establish that in the cortex of adult humans,  $^{14}\text{C}$  levels matched those in the atmosphere at the time of the individual's birth—suggesting that few, if any, cortical neurons had been produced later in life.

Frisen and colleagues teamed up with several other laboratories for a more extensive study, reported in *Proceedings of the National Academy of Sciences*.<sup>1</sup> Working with autopsied brain tissue from seven individuals born between 1933 and 1973, the investigators measured neurons from all lobes of the cortex. They again found  $^{14}\text{C}$  levels corresponding to those at the time of each subject's birth, providing strong evidence that neurogenesis in the cortex is limited to the developing brain.

They surmise that although neurogenesis in the hippocampus may play a role in some types of memory, cognitive functions

*Cortical neurons may be some of the first cells produced as the human embryo takes form.*

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such as learning and analysis are handled by cortical cells that have been in place since birth, and that in the cortex stability is favored over plasticity.

The cortex is the seat of “higher” functions such as reason and analysis and is considered the part of the brain that distinguishes humans from other species. A study reported in *Nature Neuroscience* shows that cortical neurons may be some of the first cells produced as the human embryo takes form.

Researchers led by Colin Blakemore of the University of Oxford and Pasko Rakic of Yale University identified a distinctive population of neurons emerging within the first few weeks of pregnancy. These predecessor cells begin life in the area that becomes the cortex, appearing before other neurons that are produced deeper in the brain, and migrate to positions in the cortex as the brain develops.

The predecessors also produce a different set of marker proteins, suggesting that they are a unique cell population. The finding provides evidence that the first cells of the distinctly “human” brain are present at a very early stage in embryonic development, and it is important for understanding the development of the normal brain and, possibly, many cognitive disorders.<sup>2</sup> For example, the recent findings in autism suggest abnormalities in cortical development in that disorder (see Disorders that Appear in Childhood, page 13).

The therapeutic use of stem cells depends on their ability to develop into specific cell types needed to correct a given illness by performing a specific function. According to a report in *Nature Neuroscience*, this plasticity, or “pluripotency,” has its limits.<sup>3</sup>

Researchers led by Sally Temple of Albany Medical College in New York found that the timing that governs cortical development is encoded within the progenitor cells that give rise to the neurons—not signaled by factors in the neurons’ environment. The cortex develops in layers, with neurons for each layer produced according to a predictable schedule.

The investigators found that when neural progenitor cells taken from mice were cultured in isolation, the resulting neurons appeared in the same sequence as they would in the embryonic brain. At each stage the cells lost some of their plasticity. By reducing a gene called *Foxg1*, required for cortical development, the investigators were able to reset the timing of mid-gestation but not late-gestation neurons.

The finding has important implications for stem cell therapy, suggesting that the sequence of development is programmed right from the beginning and that the cells can be diverted from their “fate” only during a narrow window of time.

### ***A Natural Response to Injury***

Many studies in animals have shown that the adult brain can respond to injury or “insult” with a surge of neurogenesis—an ability that could be exploited to treat injury from trauma or stroke if the precise steps were understood. Reporting in the *Journal of Neuroscience*, T. Yamashita and colleagues found that, after a stroke, a group of neural stem cells that normally produces only olfactory cells is able to produce new neurons in the striatum where the injury occurred.<sup>4</sup>

These new neurons proved able to form connections with neighboring striatal cells. The finding has implications for treating stroke and other neurological disorders.

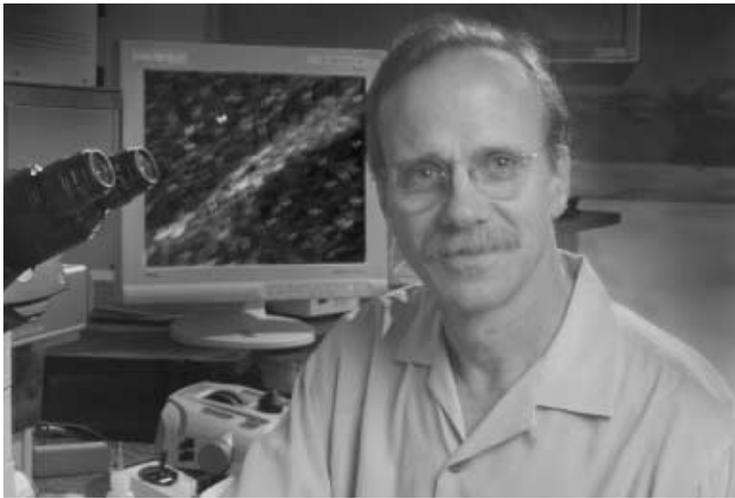
To study the role of neurogenesis in stroke recovery in humans, David Greenberg of the Buck Institute for Age Research and his research group looked for newborn neurons in human brain biopsies taken from stroke-induced brain lesions. As reported in *Proceedings of the National Academy of Sciences*, the areas around the site of injury showed molecular markers of newborn neurons—especially near blood vessels, which produce growth factors that enhance division and growth of neurons during neurogenesis.<sup>5</sup> The finding suggests that some neurogenesis

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***Neurogenesis may also be a natural response to spinal cord injury, one that could be harnessed for therapeutic purposes.***

takes place and that medications to enhance the process could be useful treatments.

Neurogenesis may also be a natural response to spinal cord injury, one that could be harnessed for therapeutic purposes. In the *Journal of Neuroscience*, Michael Tuszynski and Fred Gage of the Salk Institute and colleagues reported their finding that adult rhesus monkeys given an experimental spinal cord injury showed an increase of more than 80-fold in the number of newly divided cells.<sup>6</sup> By seven months after the injury, many of the cells had become various types of support cells; some were producing



### Neurogenesis and spinal cord injury

*A team led by Fred Gage, above, and Michael Tuszynski, both of the Salk Institute, found that new neurons occur naturally following an injury to the spinal cord. The process may inspire new therapies.*

myelin, the fatty insulation crucial to the axons of injured neurons. The work is evidence that some neurogenesis takes place to help repair spinal cord injuries, and it could be enhanced by the right therapies.

### Neurogenesis and Epilepsy

Some animal studies show that epileptic seizures stimulate neurogenesis. However, a study reported in a special neurogenesis issue of the journal *Hippocampus* shows that the newly born cells

### ***The study raises an important question: Why does the brain produce different cell types in response to different injuries?***

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grow not into replacement neurons but into glia (cells that perform “support” functions, such as producing myelin, rather than transmit signals).<sup>7</sup> Jack Parent of the University of Michigan Medical Center and his team found that rats experiencing chemically induced seizures showed a marked increase in brain cells, as indicated by a chemical that fastens onto dividing cells, for a two-week observation period after the procedure.

Because the cells developed into glia, unlike the newborn neurons that follow stroke-induced injury, the study raises an important question: Why does the brain produce different cell types in response to different injuries? Further research will shed light on neurogenesis as a means for repair and may point toward new treatments for epilepsy.

Another team led by Parent has found that neurogenesis after a seizure may be part of the problem. In human and experimental temporal lobe epilepsy, for example, a part of the hippocampus called the dentate granule layer is often abnormal. The investigators reported in the *Annals of Neurology* that in rats with prolonged seizures, progenitor cells in this layer area migrate and develop abnormally.<sup>8</sup> Although neurogenesis persists throughout life in some areas of the hippocampus, the researchers surmise that seizures disrupt the neurons’ migration, leading to faulty integration of newborn cells and possibly to recurrent seizures.

### ***Antidepressants Boost Neurogenesis at Specific Stage***

Antidepressants are suspected to increase the rate of neurogenesis in the hippocampus. But the medications currently available take three to four weeks before improving the mood of patients with depression, and about a third of patients do not respond to treatment at all. Many studies suggest that drugs such as Prozac may ultimately work by increasing the rate of neurogenesis; if the steps involved were better understood, medications could be developed to stimulate neurogenesis more directly.

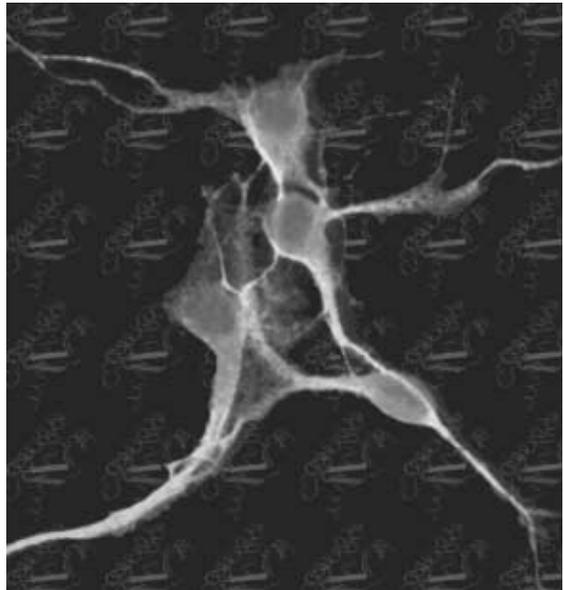
In *Proceedings of the National Academy of Sciences*, researchers at Cold Spring Harbor Laboratories reported having developed a strain of “reporter” mice with a blue fluorescent protein in the nuclei of cells derived from neural precursors.<sup>9</sup> By checking the “blue” neurons for various marker proteins, then exposing the cells to fluoxetine (Prozac), the team ascertained that stem cells at one specific stage of development are the drug’s sole target. Finding more direct ways of boosting this population of cells might result in treatments for depression that work more quickly and effectively.

## **Disease Proteins and Brain Cell Development**

Prion protein is best known for its role in causing disease: when misfolded, it is the culprit in brain encephalopathies, such as mad cow disease and its human counterpart, Creutzfeldt-Jakob disease. But studies in recent years have revealed that prion proteins are not abnormal by definition; rather, they are converted into a disease-producing form as they unfold and refold, and it is the amount of misfolded prions that determines whether or not a disease develops. Less is known about the normal prion protein’s role in brain function.

### **Beyond mad cow**

*“Researchers have learned more about the normal role of the prion protein, better known for its role in diseases. Here, the normal protein is shown in the nuclei (darker bulbs) of developing neurons (white streaks). The coiled molecular structure of the normal molecule appears in the background.”*



*The same process that determines which neural stem cells become neurons and which become support cells may explain another, more ominous observation: stem cells also have the capacity to develop into tumors.*

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Jeffrey Macklis of Harvard University, Susan Lindquist of the Massachusetts Institute of Technology, and colleagues have shown that the prion protein is plentiful in areas of the brain where neurogenesis takes place. In the study, published in *Proceedings of the National Academy of Sciences*, levels of prion protein were closely linked with the rate at which precursor cells differentiated into neurons; experimental mice that overproduced the protein had more proliferating brain cells than normal or knockout mice.<sup>10</sup> Further studies will shed light on this protein's role in the normal brain and may result in new approaches to prevent and treat prion diseases.

As reported in *Stem Cells Development*, researchers led by Kiminobu Sugaya at the University of Central Florida showed that excessive levels of amyloid precursor protein, such as are found in Alzheimer's disease, may block the production of new neurons by diverting stem cells to become astrocytes.<sup>11</sup> Stimulating cultured human neural stem cells with this protein increased their differentiation into astrocytes, while blocking the protein with an antibody prevented this differentiation.

In transgenic mice developed to produce beta-amyloid, transplanted human stem cells differentiated into glia rather than neurons. The results suggest that high levels of amyloid precursor protein may thwart the brain's self-healing efforts by changing the course of cells that would otherwise have grown into replacement neurons—a role that will have to be better understood if stem cells are to be a therapy for Alzheimer's disease and other conditions.

### **Support Cells Turn Cancerous**

The same process that determines which neural stem cells become neurons and which become support cells may explain another, more ominous observation: stem cells also have the capacity to develop into tumors. As reported in *Neuron*, a group

led by Arturo Alvarez-Buylla of the University of California at San Francisco identified a group of neural stem cells carrying a receptor for a growth factor.<sup>12</sup> An infusion of this growth factor stimulated these cells to grow excessively and show some features of tumors (see also *Nervous System Injuries*, page 32).

Meanwhile, Patricia Casaccia-Bonofil of the Robert Wood Johnson Medical School and her fellow researchers reported in the *Journal of Neuroscience* that glia may become cancerous through lack of apoptosis, or programmed cell death.<sup>13</sup> The researchers studied knockout mice missing the apoptosis-initiating p53 gene.

The absence of p53 did not automatically result in cancer. But, when the mice were given an experimental cancer-causing stimulus, their neural stem cells showed dramatic changes consistent with cancer—dividing more rapidly, for example, and not fully differentiating.

### **Notch Protein Activates Stem Cells**

The ultimate goal of stem cell therapy is to activate “endogenous” stem cells—those existing in the patient’s own body. In *Nature*, Ronald McKay of the National Institute of Neurological Disorders and Stroke reported on a model of stem cell expansion that may help realize this goal.<sup>14</sup>

Activation of a receptor known as Notch induces a chain of events that promotes the survival of neural stem cells. When adult rats were treated with a molecule that locks into the Notch receptor, they showed increased numbers of progenitor cells and improved motor skills after an experimental stroke injury. The work suggests a method for stem cell expansion both in culture and in a host animal receiving transplants, possibly even turning stem cells back on.

The stem cell field continues to flourish but the studies above indicate how much we still do not know. Directing the development of stem cells to become specific cell types (nerve cells, or glia) and not to become cancer cells remains the big challenge.

# THINKING AND REMEMBERING



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Research into thinking and remembering brought mixed results in 2006: remarkable discoveries in some areas and exposure of the need to pause and reassess approaches in others.

## Alzheimer's Disease

A hallmark of Alzheimer's disease pathology is the presence of beta-amyloid plaques in the brains of patients. Over the past decade or so, scientists have focused much of their work on these physical manifestations of the disease with the idea that if they could prevent the plaques from forming or remove them, they could mitigate the behavioral impact of the disease.

However, several groups reported data in 2006 suggesting that these plaques themselves may not be the underlying cause of the disease. The beta-amyloid plaques are aggregates of a small peptide that is clipped off a larger protein called the amyloid precursor protein and released into the space between neurons. Previous work with mice that express human amyloid precursor protein demonstrated that behavioral abnormalities, such as deficits in spatial memory, are apparent well before the plaques appear. Thus either the protein fragments are not the problem or smaller aggregations, which do not look like plaques, are damaging the neurons.

Hundreds or thousands of protein fragments make up a single plaque, but Sylvain Lesné at the University of Minnesota Medical School in Minneapolis and colleagues found that small aggregates of just 12 fragments appeared at the same time as the animals' memory started to fail.

Moreover, when the researchers purified these small clumps from the brains of diseased animals and injected them into the brains of healthy animals, the healthy animals lost their ability to learn the physical layout of a maze. The research was reported in *Nature*.<sup>1</sup>

Similarly, researchers at the Buck Institute for Age Research in Novato, California, reported in *Proceedings of the National Academy of Sciences* that if the engineered mice expressed a protein variant from which beta-amyloid cannot be released, the

mice lacked the plaques typical of Alzheimer's but still developed memory problems.<sup>2</sup>

The culprit in these animals appeared to be a different small fragment of amyloid precursor protein called C-31. The researchers conclude that the plaques that lie between the neurons may start the problem but C-31 may strike the final blow by getting inside the nerve cells. The investigators from each group hypothesize that drugs that block either the formation of the small clumps or the release of C-31 may help limit the symptoms and damage of Alzheimer's in humans.

Research involving humans also is calling into question the importance of beta-amyloid plaques as a cause of Alzheimer's disease symptoms. Scientists have known for decades that not all individuals with plaques develop the disease. To find out how common it is for healthy adults to have plaques in their brains, researchers led by David Bennett of the Rush Alzheimer's Disease Center at the University of Chicago have been following more than 2,000 healthy adults in two different communities. They reported their findings in *Neurology*.<sup>3</sup>

Study participants undergo neuropsychological testing each year to ensure that they are free of dementia at the end of their life. Yet, of the 134 participants who have died and donated their brains for postmortem evaluation, 2 had plaques in the neocortex of their brains and thus had a high likelihood of Alzheimer's disease, on the basis of current pathology criteria, and another 48 had evidence of plaques in the limbic regions of their brains, which corresponds to an intermediate risk. The only difference Bennett and colleagues found in mental functioning between these 50 patients and the remaining 84 participants, who lacked evidence of plaques, was a slight drop in the functioning of their episodic, or event-driven, memory.

Bennett's team drew two conclusions from these data. First, they suggest that even minor decreases in episodic memory may

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*Just what allows some patients with plaques to remain healthy while others, with the same amount of neuropathology, develop the disease is a key question.*

be a sign of early Alzheimer's. Second, humans generally have more neurons than are needed for daily living, which the researchers call a "neurological reserve." Thus many people can tolerate a significant amount of neuronal damage and Alzheimer's disease pathology without showing dramatic memory loss or dementia.

Just what allows some patients with plaques to remain healthy while others, with the same amount of neuropathology, develop the disease is a key question and one many researchers are now focusing on.

### **Who Converts to Full-Blown Alzheimer's**

Related research sheds light on why not all older adults who develop memory problems will develop full-blown Alzheimer's. There is no established test to distinguish between patients who will remain stable and those whose condition will deteriorate further. Such information would help physicians counsel patients and their families and develop care plans for individuals who are likely to convert to Alzheimer's disease. Two studies reported in 2006 make significant strides in that direction.

In one study, researchers at the New York State Psychiatric Institute and Columbia University in New York, led by Matthias Tabert, followed 63 healthy adults and 148 patients with mild cognitive impairment, an intermediate state between normal memory functioning and dementia. The researchers report in *Archives of General Psychiatry* that within three years 34 patients with mild cognitive impairment converted to Alzheimer's disease.<sup>4</sup>

The team found that patients with mild cognitive impairment whose only deficit was in memory were at relatively low risk of deteriorating, with only 2 out of the 20 patients in this group developing Alzheimer's. By contrast, half of the 64 patients who originally had memory problems but also other cognitive deficits developed Alzheimer's disease during the same period of time. Thus, neuropsychological testing of patients with mild cognitive impairment may differentiate between those two situations and predict who is at highest risk of further problems.

Meanwhile, researchers at the University of California in Los Angeles used physical characteristics to identify the patients with

mild cognitive impairment who were at higher risk for developing Alzheimer's.<sup>5</sup> Using high-resolution magnetic resonance imaging, they reported in *Archives of Neurology* that patients who had less volume in the hippocampus were at greater risk of converting to Alzheimer's disease than were those with greater volume. Additionally, patients who later converted to full-blown disease had more atrophy in a certain region of the hippocampus at the start of the study than the patients who remained stable. If we are going to be successful in developing treatments to either prevent or delay the onset of Alzheimer's disease, identifying these "pre-Alzheimer's" cases is essential.

## **A Cause of Frontotemporal Dementia**

Although Alzheimer's disease is the most talked-about form of dementia, it is not the only one. Frontotemporal dementia is the second most common dementia in people younger than 65. Patients with this type of dementia display abnormal behavior including personality changes and a lack of inhibition. They generally maintain their memory function, however.

Frontotemporal dementia has a strong genetic component, and mutations in a protein called microtubule-associated protein tau are already known to cause some forms of the disease. However, for patients who do not have tau gene mutations, the cause of the disease has been unknown. Two research groups found in 2006 that these patients have mutations in the gene for a growth factor called progranulin.

This gene is expressed in a wide variety of neurons in the cortex of the brain and in microglial cells, which are the immune cells of the brain. In two studies reported in *Nature*, the researchers hypothesize that progranulin is important for neuronal survival and that loss of even one copy of the progranulin gene is sufficient to cause neurodegeneration.<sup>6,7</sup> In animal models, progranulin appears to induce the expression of other growth factors, which might contribute to cell survival.

The identification of the mutation that underlies this type of frontotemporal dementia opens avenues for the development of new therapies for these patients.

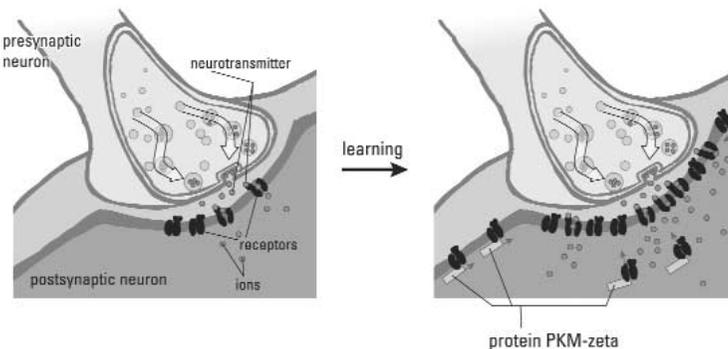
## In Normal Memory, a Big Step Forward

Scientists have long hypothesized that memories are stored via changes in the strength of the synaptic connections between neurons. If so, then when a memory is laid down the strength of the synapse increases, as does its ability to communicate with its neighbor.

This process is called long-term potentiation, or LTP. Three studies now provide key evidence that LTP is the neural foundation that gives rise to memory.

Researchers have focused on three criteria: blocking LTP with chemical inhibitors should prevent learning, learning a specific task or information should invoke LTP in the brain region that handles that type of information, and wiping out LTP with chemicals after learning should cause amnesia and eliminate the learned behavior.

Previous research demonstrated that the first criterion was met. In one of the experiments in 2006, Jonathan Whitlock and colleagues at the Howard Hughes Medical Institute and the Massachusetts Institute of Technology trained rats to avoid the dark region in their cage by giving them a mild electric shock when they entered it. The group reported in *Science* that as the animals learned this spatial information, LTP occurred in the animals' hippocampi, which is the site of spatial learning in rodents.<sup>8</sup>



### Thanks for the memory

Researchers have found that long-term potentiation, which gives rise to memory, depends on a protein called PKM-zeta. When the protein is blocked, rats forget behavior they have learned.

Agnès Gruart of the Universidad Pablo de Olavide in Sevilla, Spain, reported similar results in the *Journal of Neuroscience*.<sup>9</sup> That team found that learning induced LTP in the hippocampus of mice and that drugs which prohibited neural transmission blocked both learning and LTP formation.

A group led by Eva Pastalkova at the SUNY Downstate Medical Center in Brooklyn, New York, took this idea one step further in a study they reported in the same issue of *Science*. They showed that when LTP was chemically reversed, the animals forgot their learned behavior.<sup>10</sup> The treatment, however, did not preclude all synaptic transmission, nor did it prevent subsequent learning.

These studies provide important evidence that the longstanding hypothesis of how memories form is likely correct.

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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 rewire 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.

**A**lthough 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 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 to 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.

## **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.

## **THE GOALS**

### **Combat the devastating impact of Alzheimer's disease.**

In Alzheimer's disease, a small piece of the amyloid protein 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 to 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, and 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 10 to 15 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 throughout 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 10 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 because of 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 nonfunctional 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.

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