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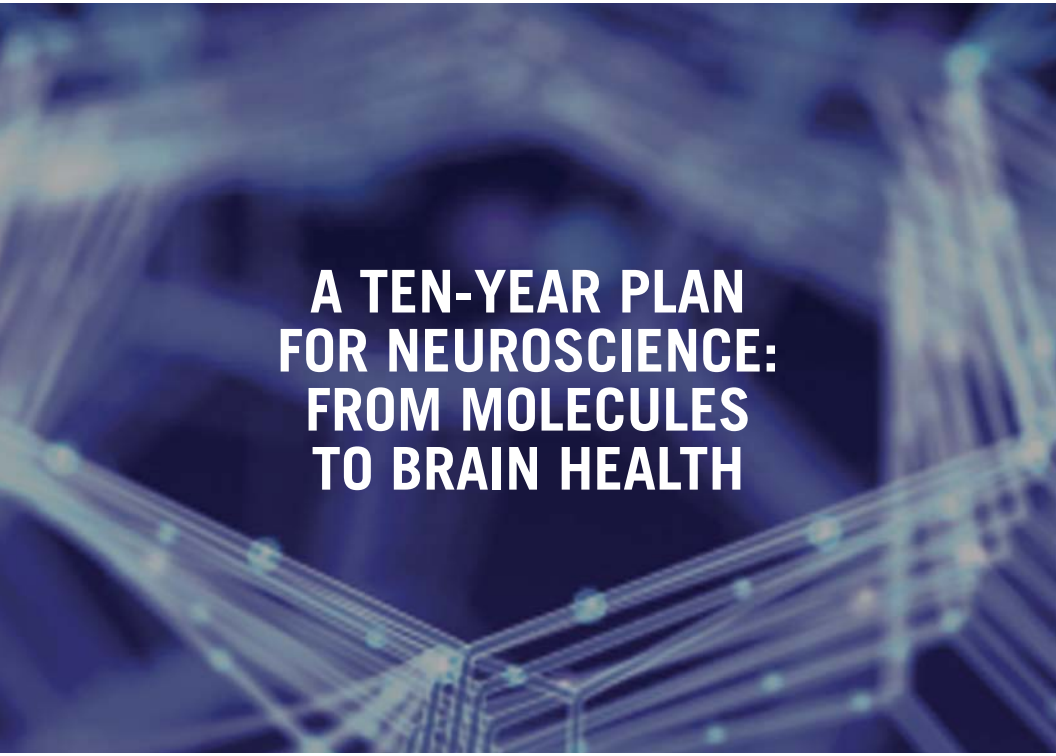

A TEN-YEAR PLAN FOR NEUROSCIENCE: FROM MOLECULES TO BRAIN HEALTH

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This document makes three key points: (1) Neuroscience has made remarkable strides in the forty years since it began to coalesce as a recognized field. Yet gains in the diagnosis and treatment of brain disorders remain hard-won because of the extraordinary challenges of understanding the human brain. (2) These scientific hurdles notwithstanding, the staggering global toll of brain disorders urgently demands effective solutions. Indeed, the profound, negative consequences of brain disorders are growing steadily as humans have begun to live longer, as old scourges such as infectious disease have begun to recede, and as globalization has exerted increased pressure on human capital formation and performance. *The cost of inaction would prove staggering.* (3) It is time for investment and a concerted effort. Powerful new and emerging scientific tools make possible a significant acceleration in both discovery and applications to disease. Important new ideas and tools have come not only from neuroscience itself, but also from genetics, chemistry, physics, engineering, computational sciences, and other disciplines. Significantly, advances in fields ranging from genomics to optics to magnetic resonance imaging have not only strengthened neuroscience, but have also engendered cross-disciplinary collaborations and new modes of scientific organization that free our imaginations to examine important problems in a whole new light.

The plan that follows touches on both fundamental and disease-oriented neuroscience. In reality, there is no bright line between the two. We cannot predict when a basic discovery will lead rapidly to clinically relevant insights, nor does the flow of discovery move unidirectionally from basic to applied. Rather, these large domains fertilize each other. Indeed, despite our intense shared desire to prevent, treat, indeed to cure devastating brain disorders, the scientists involved in developing this plan recognize that a premature narrowing of focus to clinical applications could paradoxically slow the discovery and development of the interventions we all seek. That said, it is critical to recognize opportunities for clinical translation as they emerge, and to work in new collaborative ways across academia, government, and industry to remove current obstacles to the development of accurate diagnostic tools and safe and effective treatments.

This document makes a strong case that brain research is at a critical inflection point, and is worthy of substantial support even in challenging economic times. Indeed, given the large and growing burden of brain disorders, *there is an enormous cost to inaction*.

This planning process has been organized and supported by the Society for Neuroscience, with significant help from the National Institutes of Health that support brain research. Many other research organizations and individual scientists have contributed, both through organized discussions such as that held by the US Institute of Medicine Neuroscience Forum and by written communications. The plan that follows is thus a joint working document, meant to advance neuroscience, rather than the consensus of any one organization.

The identification of shared scientific goals invariably favors "top-down" thinking. This plan, developed collaboratively by many scientists, highlights large shared themes, the development of a large-scale intellectual infrastructure, tool building, and a limited number of feasible goals that appear today to be most pressing. The scientists who have contributed to this plan have repeatedly stressed, however, that execution of this plan should serve to strengthen, rather than crowd out, work coming from smaller laboratories and hypothesis-driven research. Indeed, shared tools, shared information, and a new collaborative ethos should combine to reinforce all efforts to address the challenges posed by the human brain.

INTRODUCTION

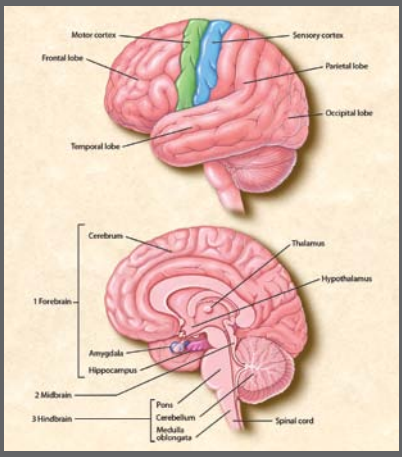
I. THE MOST COMPLEX ORGAN

The human brain is the most complex object of study in the history of science. That complexity should come as no surprise since the brain underlies all perception, thought, emotion, purposeful action, language, and imagination. The human brain permits not only the development of rich and subtle ideas, practical applications, moral systems, and artistic expression, but also their cultural transmission across generations. In ways that we do not yet understand, the brain is the substrate of our conscious awareness and thus all our subjective experience, including our sense of identity.

The complexity that supports the extraordinary capacities that we enjoy as human beings creates enormous challenges for scientists who would understand our brains. Neuroscientists face these challenges whether trying to understand fundamental neural processes or attempting to comprehend the dreadful disorders that result when neural processes go awry. A brief introduction to the brain's dazzling complexity will begin to reveal the challenges.

Compared with all the other organs that constitute our bodies, the brain contains an extraordinary number of distinct types of cells. The thousands of cell types in the nervous system include both neurons and glial cells. Neurons are the principal cells that process information and generate outputs. Glia once were thought to perform only supporting functions, but are now recognized to play significant roles in health and disease. In the aggregate, these cells utilize the information encoded by approximately 80% of the genes in the human genome, a higher percentage than that of any other tissue. This genomic information directs the production of an even greater and more diverse array of RNA and protein molecules, the building blocks of cellular structure and function.

The precise structure and roles of each of the many thousands of types of neurons reflect the pattern of genes each expresses at rest and the changes in gene expression that occur in response to the chemical and electrical signals that characterize communication in the nervous system. Each type of neuron has a highly adapted morphology and a typical location in the brain that positions it for communication via a characteristic pattern of connections—synapses—with other neurons. It has been estimated that the neurons within the human brain form nearly 100 trillion synapses. These connections, stunning in their number, are the basic building blocks of neural circuits, the substrate upon which the computational processes of the brain operate. Local patterns of synaptic connections give rise to small circuits, and these, in turn, give rise to the large-scale circuits that connect diverse and often distant regions of the brain and spinal cord. It is



THE BRAIN

The brain is the body's most complex organ. It can be divided into four sections, or lobes, and many internal structures. Functions, such as vision, hearing, speech, and movement are distributed in selected regions. The brain supports our highest intellectual capacities — thinking, planning, and problem-solving. It helps us remember events, regulates sleep, arousal, and temperature, and controls respiration and heart rhythms.

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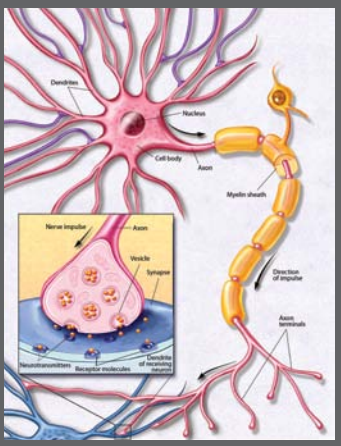

THE NEURON

The brain contains specialized cells called neurons, which transmit electrical and chemical signals. Neurons within the human brain form nearly 100 trillion connections — synapses— with each other. This nearly incomprehensible number of synaptic connections forms the basic building blocks of neural circuits that underlie the computations by which the brain processes information.

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activity within both local and large-scale circuits that ultimately gives rise to thought, emotion, and behavior. Thus, disease processes that affect the structure and function of neural circuits produce the symptoms of different brain disorders.

As if their enormous numbers do not create enough complexity, synapses in the nervous system are anything but static. As cells and synapses respond to environmental stimuli, neural and hormonal signals, and drugs and other chemicals, they participate in finely tuned and increasingly well-understood processes of "synaptic plasticity." Synaptic plasticity increases or decreases the strength of signals at individual synapses, produces new synapses, and prunes others. In so doing, plasticity alters neural networks and thus permits long-term alterations in information processing and behavior. Synaptic plasticity is the key mechanism by which memories are encoded and stored and is critical to refining adaptive patterns of connectivity during brain development. Pathologic excesses of synaptic plasticity may lie at the heart of post-traumatic stress disorder, significant forms of chronic pain, and addictive disorders. Failures of plasticity almost certainly occur early in Alzheimer's disease. Abnormal neurodevelopmental processes that involve synaptic plasticity may also contribute to such disorders as autism, schizophrenia, attention deficit hyperactivity disorder, specific learning disabilities such as dyslexia, and forms of epilepsy.

If we are to understand the gamut of brain disorders that afflict humanity, it will be necessary to understand pathological processes at multiple levels

of organization in the nervous system: molecules, cells, synapses, circuits, computation, cognition, and behavior. Even in superficially "simple" cases in which a brain disorder results largely from damage to a single cell type, symptoms and treatment must be understood at multiple levels. In Parkinson's disease, for example, which begins primarily with the death of dopamine-producing neurons of the midbrain, the multiplicity of symptoms and the limitations of treatment reflect complex molecular and cellular adaptations within the multiple circuits influenced by the affected midbrain dopamine neurons.

Brain complexity is a major scientific challenge, but human neurobiology must also take into account the inaccessibility of our brains. In contrast to most other organs, living brain tissue normally lies beyond the reach of scientists and clinicians, for both ethical and pragmatic reasons. There is an appropriately high ethical barrier to the sampling of tissue from the brain, an organ that functions via unique circuits and nodes—rather than in bulk like the liver or kidney—and that does not normally regenerate. Thus, even for clinical purposes, brain biopsies are generally reserved for dire circumstances such as the presence of brain tumors, and the use of recording or stimulating electrodes is limited to situations in which other alternatives have been exhausted. Even if it were ethically permissible to sample brain tissue more routinely, the fact that many brain disorders result from abnormal connectivity or signaling within distributed neural circuits arising from many different cell types and brain regions means that a small local tissue sample might yield little useful information. In addition, of course, the brain is encased in a hard and generally opaque skull, and is further protected from the rest of the body by a blood-brain barrier that maintains the environment needed by neurons and glia to ensure proper signaling within neural networks. Of necessity, therefore, most studies of the human brain are indirect, relying on such technologies as diverse forms of noninvasive imaging, electroencephalography, magnetoencephalography, and transcranial magnetic stimulation.

II. THE BURDEN OF BRAIN DISORDERS DEMANDS PROGRESS

Given such hurdles, one might ask why we must persevere in the pursuit of neuroscientific discovery. Part of the answer, of course, lies in the deep desire of humanity for self-understanding. But there is a more urgent motivation: the need to conquer brain disorders. The staggering toll of brain

disorders has only recently begun to come into full view. The reasons for long-standing underestimates of this burden are multiple. Historically, a failure to recognize the neural basis of all human thought, emotion, and action has produced significant misunderstandings of neuropsychiatric disorders. People with brain disorders ranging from epilepsy to schizophrenia to addiction have been, and too often remain, objects of stigma and fear. Medical researchers have long focused their attention and resources on understanding and treating direct causes of mortality, such as infectious disease, heart disease, and cancer. As human life spans have increased, and as older scourges such as infectious diseases have increasingly come under control, a more sophisticated understanding of the negative effects wrought by disease on individuals and societies is emerging. The World Bank and the World Health Organization (WHO) have developed widely influential models that define *disease burden* as a function of both premature mortality and healthy years of life lost to disability. The WHO now calculates the global burden of disease in terms of a measure called the disability adjusted life year (DALY). While historically belated and methodologically challenging, recognition of the costs of disability has finally highlighted the harm wrought by brain diseases.

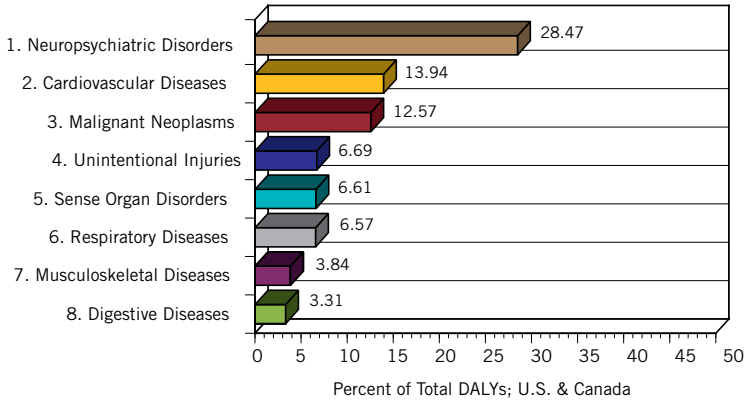
Of course, many brain diseases, ranging from brain tumors to Alzheimer's disease, are ultimately lethal. The terrible path to death produced by neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) is well known. Suicide—for which depression, schizophrenia, and substance use disorders are the leading risk factors—is among the top ten causes of death in many countries, and among the top three causes of death in youth and young adults in developed countries, including the United States. It is not widely appreciated that there are nearly two suicides for every homicide in the United States, and that suicide recently has surpassed combat death as a cause of mortality in the military.

Although brain disorders do cause premature mortality, their greater contribution to disease burden results from disability. According to the WHO, neuropsychiatric disorders are the leading aggregate cause of disease burden in the United States and Canada (28.5% of DALYs; see Figure 1), and sensory disorders contribute an additional 6.6%. Mental, neurological, and substance use disorders represent five of the top eight causes of DALYs in the US and Canada (see Figure 2).

Despite advances in recognizing the costs of brain disease to society, the true burden of brain disorders is likely still underestimated. In particular, we lack good measures for the corrosive effects of brain disorders on human capital formation. Human capital represents the knowledge, competencies, and personal characteristics that enable individuals to contribute to society, economically and otherwise. Disorders associated with abnormal brain

FIGURE 1

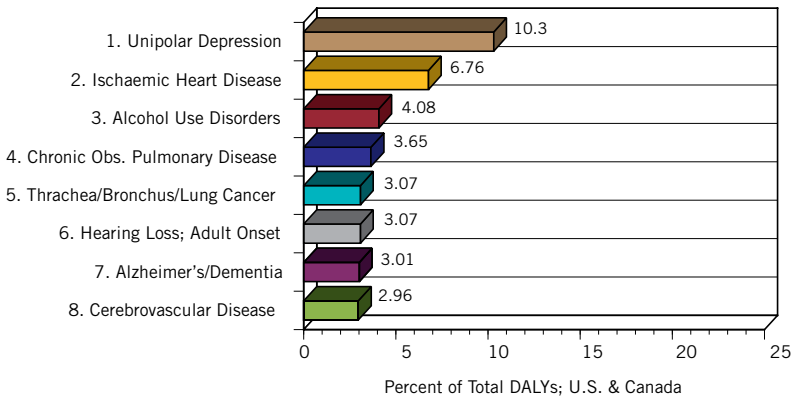
Burden of Disease: Lead Contributing Disease Categories to DALYs



Data courtesy of WHO

FIGURE 2

Burden of Disease: Leading Individual Disease/Disorder Contributors



Data courtesy of WHO

BEYOND STATISTICS: NEUROBIOLOGICAL POWs

Among the tragic consequences of war are the large number of soldiers who suffer severe and debilitating brain disorders. Many soldiers who have served in Iraq and Afghanistan return as virtual prisoners of war, their invisible prisons constituted by the severe impairments and suffering caused by traumatic brain injuries (TBIs), post-traumatic stress disorder (PTSD), depression, suicidality, chronic pain, and substance use disorders (SUDs). The widespread use of improvised explosive devices (IEDs) has made traumatic brain injuries the signature wounds of these recent wars. Damage may occur in many brain regions, but especially within the prefrontal cerebral cortex, a region that permits a person to exert "cognitive" control over thoughts, emotions, and impulsive behavioral responses. As a result, TBI often robs its victims of the ability to manage the ordinary stresses of life, or to persist in the tasks necessary for success at work or school. These impairments affect not only the returning soldiers, but also their families. Too often, the broader society misinterprets their behavior and fails to support and sustain the very individuals who were wounded defending us all.

Post-traumatic stress disorder occurs when brain circuits that under normal circumstances produce adaptive avoidance of direct threats to safety are "hijacked" by intense traumatic experiences outside normal human experience. Even small reminders of the trauma can produce intrusive reliving of the original experience, causing victims to avoid not only true dangers but sometimes to withdraw from life. When TBI and PTSD co-occur, as they often do, symptoms may be difficult to disentangle, and both conditions increase the risk of depression. The costs of these brain disorders are staggering: they include direct health care expenditures, many years of lost productivity for these young soldiers, and diversion of their caregivers from the workforce. This ten-year plan was driven by a commitment to use the best science to liberate these virtual prisoners of war, recognizing that neuroscience offers the best hope for those struggling with these invisible wounds of war.

development degrade human capital formation by impairing the ability of children to learn in school, to develop skills, and to successfully interact with peers. Neurodevelopmental disorders include generalized intellectual disability (formerly known as mental retardation), autism, many childhood epilepsies, attention deficit hyperactivity disorder (ADHD), specific learning disabilities, and early-onset mood and anxiety disorders. In more severe cases of developmental disorder, individuals are unable to live independent lives. In the majority of cases, however, individuals can live independently but cannot contribute fully to their families or to society.

As human longevity increases, so does another category of brain disorders, the neurodegenerative disorders. These include Alzheimer's disease, Parkinson's disease, frontotemporal dementia and many others. As many as 5.1 million Americans now suffer from Alzheimer's disease, and if effective interventions are not developed, this number will grow rapidly as our population ages. After the age of 65, the risk of Alzheimer's disease doubles approximately every five years. It has been estimated that, by the age of 85, the risk of significant dementia due to Alzheimer's disease may be in the range of 25–40%. Perhaps 35 million people worldwide have Alzheimer's disease today, and, because of the successes in extending life spans worldwide, by 2050 more than 100 million people may have Alzheimer's disease. Recent advances in earlier detection of Alzheimer's disease underscore the opportunity and compelling need for earlier, effective interventions to preempt this looming catastrophe.

A third category of brain disorders, neuropsychiatric disorders—including autism, schizophrenia, bipolar disorder, anxiety disorders, and depression—produce profoundly negative effects on health status, on the ability of young people to learn and to achieve their potential, and on the ability of adults to work fully and productively. Major depression is the leading individual contributor to DALYs in the United States, surpassing even ischemic heart disease. Unlike many other chronic medical disorders (e.g., hypertension, type 2 diabetes, or cardiovascular disease), neuropsychiatric disorders are chronic disorders that begin early in life. Many neuropsychiatric disorders, such as autism, have a chronic unremitting course; others, like depression, tend to begin early and to recur multiple times across the lifespan. In a major epidemiologic study, 50% of adults with a psychiatric disorder described onset by age 14; 75% by age 24. As a result, neuropsychiatric disorders devastate human capital formation and adult productivity and explain much of the tragedy of teen and young adult suicide.

III. A TIME FOR ACTION

Even given the staggering toll exacted by brain diseases, we still must ask: what new developments warrant a highly focused, well-funded, large-scale push at this time, given the challenges of brain science? In answer we point to several highly significant developments that are revolutionizing the landscape of research: (1) the advent of powerful new tools and technologies, (2) the emergence of significant new ideas and understandings, and (3) the development of new forms of organization for the research enterprise based on enhanced interdisciplinarity, and on collaborations made possible in large part by advances in computing and communication. New forms of organization include successful large-scale efforts to identify disease genes and to map the wiring diagram of the brain ("connectomics"). These efforts are based on large technological platforms and computation that enable discovery on a scale not hitherto seen in neuroscience.

Tools matter. Progress in optics yielded the telescope that permitted Galileo to observe four of Jupiter's moons, and thus to change forever the concept of how the universe is organized. The microscope permitted Leeuwenhoek to open up a new, previously invisible world by observing microbes. Neuroscience is the beneficiary of many important new tools, some influencing all of biology, others more focused on brain science. The fields of genomics (the systematic study of full DNA sequences of organisms) and genetics (correlating DNA sequence variation with phenotypic traits, both normal and disease-related) have changed all of biology. For neuroscience, genomics has provided a catalogue, literally a "parts list" for cells, and has permitted comparisons of genes expressed in the human brain with those of other animals. Of enormous significance, the application of genomic methods to genetics is beginning to yield critical clues for understanding the neurobiology of disease. Insights from genomics, combined with molecular biology (which involves the ability to isolate and manipulate DNA sequences, and more recently to design DNA sequences *de novo*, and to express them in microorganisms, animal models, or human cells) have created powerful new tools. For example, engineered genes inserted into the cells or into selected cells of animals can serve as fluorescent markers of chosen cell types or identify those neurons activated by a particular stimulus. Other engineered genes permit scientists to activate or inactivate specific cells and circuits in animal models. The exploding field of "optogenetics" for example, gives investigators the ability to activate specific

brain circuits with exquisite precision using beams of light. In addition, gene therapy, after a long, frustrating period of development, has begun to deliver on its promise by restoring sight to individuals with inherited degenerative disorders of the retina and therefore paving the way for its application to central nervous system disorders.

Noninvasive tools for imaging the brains of both humans and animal models constitute a powerful and still rapidly-growing suite of technologies that permit observation of the living human brain at work, both in health and in illness. Indeed, progress is accelerating in the development of imaging technologies across many orders of magnitude of scale. These range from remarkable new tools for microscopy to increasingly powerful magnets for MRI that confer the ability to study the structure and function of large-scale neural circuitry with breathtaking precision. Microscopy is evolving rapidly, enabling the imaging of brain tissues, cells, subcellular structures and even molecular complexes at increasingly high spatial and temporal resolution. Moreover, microscopy can now be performed not only in fixed preparations, but in living tissue as well, including in the brains of awake-behaving animals over long periods of time. This constitutes a profound revolution, which is likely to continue in the next decade, and that will place the technologies of imaging at the center of research in neuroscience, including human neuroscience. That progress is due, in no small part, to the increasingly frequent collaborations among basic neuroscientists, clinicians, chemists, physicists, engineers, mathematicians, and computer scientists.

Neuroscience is itself a highly interconnected, interdisciplinary endeavor that brings a wide variety of approaches together in the service of understanding the functioning of the nervous system in health and disease. The brain is the organizing principle for a community of scientists and clinicians with diverse disciplinary backgrounds. Indeed, there is no linear exposition of a broad ten-year plan that could do justice to the interconnectedness of neuroscience. In order to make its components more accessible, however, this plan has been organized into scientific clusters, the first four more related to fundamental neuroscience and the latter two more related to brain disorders. However, the more basic areas also illuminate disease and those bearing more directly on disease pose important problems for fundamental neuroscience. These basic clusters are: (1) molecules, cells, and synapses (2) circuits (3) development, plasticity, and repair (4) behavioral, cognitive, and systems neuroscience. The more disease-related clusters are (5)

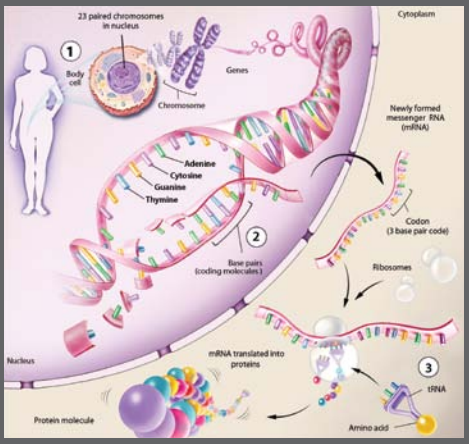
neurobiology of disease, which examines the fundamental mechanisms of diseases and therapies, and (6) clinical neuroscience, which involves the study of patients. With respect to clinical neuroscience, older practices have often divided neurology from psychiatry and psychology. In recent years, it has become clear that the putative boundary between neurologic and psychiatric disorders does not serve progress, because it reflects historical patterns of clinical practice rather than meaningful scientific differences. As a result, clinical neuroscience is presented here in a unified format.

As this plan emerged from the efforts of a large number of scientists, several themes kept emerging that cut across the clusters. To highlight important new approaches that help tie modern neuroscience together and that help answer the question "Why invest in neuroscience now?," we first present these shared major themes, and then refer to them throughout the plan.

SHARED MAJOR THEMES

1. GENETICS

The "blueprint" for each human being lies in the approximately 3 billion base pairs of DNA in our genomes, divided into 23 chromosome pairs. Much of human diversity, including disease risk, derives from differences in the DNA sequences that we inherit from our parents (or, less commonly, from new mutations that may occur during the formation of gametes). This genetic information is "read out" in the form of RNA and, subsequently, proteins, in an intricate dance with environmental factors and chance during development and, indeed, throughout life. Our ultimate traits, including our bodily features, our behavioral tendencies, our risk of various illnesses, our ability to heal, and our responses to treatments, are highly influenced by the sequence variation within each of our genomes. With the late-twentieth-century Human Genome Project as a fulcrum, vastly improved and cheaper technologies for sequencing DNA and detecting its expression continue to emerge. The first human sequence cost $3 billion, approximately $1.00 for each base pair. As of today, the cost of sequencing a full human genome, far more rapidly and far more accurately than ever before, has dipped below $5,000, a drop of nearly one million-fold from 10 years ago, with a corresponding reduction in speed from years to hours. Breakthroughs in computing and data analysis, and changes in how genetics research is organized, have made possible striking advances



GENETICS

Inside every cell is our body's "blueprint," DNA. Our DNA is organized into 23 pairs of chromosomes, one set inherited from each parent. Each chromosome has genes – discrete segments of DNA that contain instructions for making all the proteins necessary for life.

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in understanding brain disease. Much current success depends on the formation of large consortia that share enormous databases of patient information and sequence data. Genetics has revolutionized biological approaches to many neurodegenerative disorders, including Huntington's disease, Parkinson's disease, heritable ataxias, Alzheimer's disease, and frontotemporal dementia. Identification of genetic variation associated with disease is beginning to provide critical clues to what goes wrong in the brain in many devastating neuropsychiatric disorders that are influenced by a large number of different genes, including forms of cognitive disability, autism, schizophrenia, and bipolar disorder. Specific goals for genetics are found embedded throughout this plan.

2. EPIGENETICS

Genetics focuses on the correlation of DNA sequence variation with observable traits; epigenetics is the study of an important set of mechanisms that contribute to deciding which genes are expressed ("read out") to produce RNA and proteins that are the key building blocks of cells. Regulation of gene expression plays a key role in determining which traits actually emerge from an individual's genome. While the study of how genes are activated or silenced is decades old, there has been a new burst of excitement about epigenetic mechanisms of gene regulation because these could explain very long-lived changes in brain function that result from environmental influences.

Every cell in the brain contains the same DNA sequences that characterize the entire individual person. During the course of development, in each of the brain's myriad cell types, some of these genes are silenced and others are activated. The differential expression of a common genome is what produces the diversity of cell types that make up all of our organs. Epigenetic regulation refers to the covalent modification of (that is, the formation of chemical bonds within) DNA itself, or covalent modification of the histone proteins that bind DNA within the cell nucleus. Long-term or permanent epigenetic modifications have long been recognized as a key mechanism of differentiation during early development; notably, there is new recognition that post-developmental environmental effects, ranging from stress to illness to the use of both therapeutic and abused drugs, can regulate the expression of genes through epigenetic mechanisms. Some of these changes in gene expression may exert long-lived effects on physiology and behavior and thus have great importance to brain health and to treatment development. Drugs that might influence epigenetic regulation of gene expression are already being investigated for the treatment of memory disorders and depression.

3. THE CONNECTOME: THE "WIRING DIAGRAM OF NERVOUS SYSTEMS"

Given the enormous number of neurons in the human brain, and the even greater number of synapses it has been a challenge to develop a complete and accurate wiring diagram. Each neuron may makes on average a thousand synapses, and some cell types make exponentially more. Yet, given the fundamental role of neural circuits in normal function and disease, wiring diagrams of both important model organisms and humans are unquestionably needed for progress. Exciting new tools have given birth to a field known as connectomics. A connectome is a comprehensive description of the neuronal connections within a specified region of neural tissue. Ultimately, this can be extended from a given brain region to the entire brain of an organism. The complete connectome of any organism will represent a high-resolution map of all the neurons in that nervous system and their synaptic connections. A complete human connectome represents a highly ambitious goal that can fairly be analogized to the moonshot. As connectomics progresses, however, it should yield significant insights into human brain disorders, most obviously those, ranging from learning disorders to autism to schizophrenia, that are thought to result from developmental abnormalities in brain circuits.

The enormous range of physical scales relevant to brain connectivity warrants that a distinction be made among macro, micro, and meso scales as various connectome projects proceed. A macro-connectome describes all long-distance connections. This is now feasible to attempt for an entire human brain at a scale of ~1 mm. A micro-connectome describes all neurons, axons, dendrites, synapses, and glial cells in a domain up to ~1 mm in size, as can now be attempted in laboratory animals. A meso-connectome provides a bridge between macro- and micro-connectomes by describing both local and long-distance connections. The patterns of connectivity will enable us to understand how neurons are wired by synapses and how microcircuits form and participate in neural networks (Human Connectome: http://www.humanconnectome.org/consortia/).

4. NEURAL STEM CELLS

The human nervous system is composed of an extraordinarily diverse set of distinct types of neurons and glia. Each neuron type has its own unique roles to play in the nervous system. It is the distinct characteristics and functions of each neuron type within the circuitry of the brain and spinal cord that make possible the extraordinary capacities of the nervous system. It is also these distinct and specialized characteristics that render particular neuron types

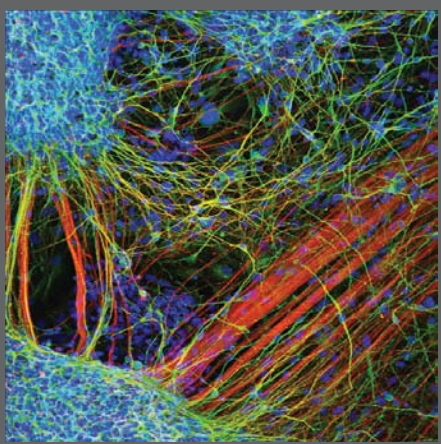

Image of neurons derived from schizophrenic patients at 400x magnification. The neuronal marker βIII-tubulin is red, the dendritic marker MAP2AB is green and nuclei are labeled blue.

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In recent years, scientists have been able to derive embryonic stem cells (ESCs) from early stage embryos. More recently, steadily improving methods have permitted scientists to "reprogram" adult cells into stem cells, thereafter called induced pluripotent stem cells (iPSCs). The application of stem cell biology to disorders of the nervous system is especially important. Physiological and biochemical studies of distinct neuronal types have been facilitated by the ability to isolate and study these cells in the laboratory. Most studies have perforce focused on neurons isolated from developing rat and mouse brains; it has not been routinely possible to isolate analogous populations of human neurons, or to study fully developed brain and spinal cord neurons outside of animals, because they are too delicate to be extracted and grown in "tissue culture." Scientists, therefore, only have had a limited ability to extend findings from rodent cells and whole nervous systems to the human brain, either in health or in disease states. Recent advances in stem cell biology now offer the potential to provide an inexhaustible supply of diverse neural types, enabling previously impossible investigation of otherwise inaccessible cell types for studies of nervous system development, function, degeneration, and routes to therapy. For example:

(1) All the cells in the body of a patient with a genetically influenced brain disease share the same genome. Thus, it is now possible to grow readily available cells such as skin cells from patients in culture and to produce pluripotent stem cells from them by inserting a small number of genes into those cells by viral or chemical means. As we learn to differentiate these stem cells into relevant nervous system cell types, we can literally recreate the cellular aspects of a disease in a petri dish. Scientists will be able to dissect how cell function goes awry, engineer replacement cells and equally important, use the cells to screen candidate drug therapies.

(2) For some neurodegenerative diseases like Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), or spinal muscular atrophy (SMA), or for traumatic spinal cord injury (SCI)—all conditions in which the

most prominent symptoms and disabilities are caused by the degeneration or damage of a limited number of cell types—the ability to differentiate a patient's own cells into replacement cells (e.g., the degenerating midbrain dopamine neurons for PD, or cerebral cortex ["corticospinal"] motor neurons and spinal motor neurons for ALS and SCI) would be a major step toward a transformative treatment or cure. This would require a deep and rigorous understanding of the molecules and genes that direct the development and function of specific types of clinically relevant neurons. Cell-based therapies are more challenging to conceptualize for disorders that involve multiple cell types—e.g., stroke or traumatic brain injury (TBI)—so these are important longer-term goals for developmental and regenerative neuroscience. This is not science fiction. In the decade since human embryonic stem cells (hESCs) were first isolated, improved derivation and differentiation techniques have resulted in the first FDA-approved clinical trials of ESC-based therapies for spinal cord injury, Stargardt's macular dystrophy and age-related macular degeneration.

(3) In addition to contributing to the generation of clinically relevant neuron types from stem cells, understanding molecules and genes that control the proper development, growth, and connections of distinct types of neurons will be critical to the development of therapies for traumatic injuries of the CNS (e.g., SCI and TBI), and to therapies that control or reverse the growth of brain tumors and other nervous system tumors. For example, in the case of spinal cord injury, understanding how to regenerate connections across the injury site will likely lead to new and potentially transformative treatments for the patient's damaged neurons, using either the patient's existing adult stem cells or neurons derived from stem cells in the laboratory.

either vulnerable to, or resistant to, different diseases and injuries, whether resulting from genetic risk, trauma, infections, the dysfunction of glial supporting cells, environmental toxins, or underlying medical conditions. As a result, in many diseases or traumatic brain or spinal cord injuries, unique and stereotypical sets of neurons are affected, causing the symptoms and

disabilities associated with these distinct conditions. Improving understanding of the development, functions, and vulnerabilities to degeneration and damage of distinct neuron types will result in new and better approaches to the prevention and treatment of human nervous system disorders.

In contrast with fully differentiated human neurons, stem cells retain the potential to divide (and thus replicate themselves) and to differentiate into many different types of cells during processes of development, growth, or tissue repair. The best-known stem cells are those of the embryo, which ultimately give rise to every one of the highly diverse cell types in the body. Some differentiated tissues retain so-called adult or somatic stem cells (often called progenitor cells), which cannot generally differentiate into the full diversity of adult cells but rather into the more limited repertoire of cells needed for the tissue in which they reside. (Within the brain, only a very limited number of new neurons can be generated during adult life, restricted to some regions of the hippocampus and olfactory bulb.)

5. "SYSTEMS BIOLOGY" AND BEYOND: PUTTING THE NERVOUS SYSTEM TOGETHER AGAIN

The burgeoning approaches to global discovery ("omics") of the DNA blueprints and building blocks of the nervous system, including its myriad cell types and their diverse RNAs, proteins, small signaling molecules, lipids, sugars, and metabolic intermediates, raise the central question of how we can use these extensive "parts lists", to inform deep understanding of the nervous system, of disease, and to produce therapies. Over the last decade, beginning with research on cells simpler than neurons, a group of conceptual approaches have emerged under the banner of "systems biology." Systems approaches are based on the use of sophisticated model building using mathematical and computational tools to holistically reconstruct biology from components.

Such models must then be rigorously tested using such approaches as systematic use of RNA interference to block the translation of individual mRNAs, diverse genetically-engineered animals, the use of powerful tools to chemical biology to produce selective new small molecule probes of function, or the use of new physical tools and microscopy to probe the interactions between molecules. For example, "systems" approaches will likely prove necessary if we are to transform reams of correlative data from modern chip or DNA sequencing analyses of genetically complex disorders

into useful understandings of pathogenesis and ideas for treatment development. Examples are beginning to emerge in which sequence variation in different parts of the genome point toward shared pathogenic mechanisms in some heterogeneous disorders, such as autism. For example, in autism spectrum disorders, a small number of individuals from different families harbor genetic mutations in diverse regions of the genome that affect different synaptic membrane proteins. What is exciting is the recognition that some of these proteins interact in synapses and thus may represent different pathways to a spectrum of human disorders. Transgenic mouse models are beginning to test these hypotheses. Should findings of this type prove generalizable, even to a moderate degree, they could direct the design of new therapies to relevant pathways within cells.

6. NEW FORMS OF SCIENTIFIC ORGANIZATION

The generation of ambitious global data sets for neuroscience requires different systems of organization than the traditional small academic research lab. The resulting data sets, and in many cases, computational tools, produce substantial benefits for the entire field of neuroscience, including small academic laboratories engaged in hypothesis-driven research. Modern genomics and genetics are paradigmatic of one new type of large-scale organization of discovery. These closely related fields generate enormous data sets that require vast computing power and deep computational expertise to interpret. A cornerstone of progress in genomics that became a critical cultural norm within the human genome project is the rapid and open sharing both of data sets and of computational tools. Such openness, which is beginning to spread to other areas of discovery, is a necessary engine of progress. Without the widespread and open dissemination of data and of tools, many important discoveries—including some discoveries related to disease risk—would not be made. The critical clues would lie buried and unused in massive data archives.

Of course, reliance on large data sets extends far beyond the identification and comparison of DNA sequences. Such data sets include diverse approaches to gene expression data, proteomics (studies of the identity, structure, or function of all of the proteins within a cell type, organ, or whole organism), connectomics (large-scale neural “wiring diagrams”), and phenotypic data, including clinical data.

Beyond the genomics community, there have been several significant experiments with alternative forms of organization. The Alzheimer's Disease Neuroimaging Initiative (ADNI), for example, is a partnership that involves government (NIH), industry, and several foundations. Its central goal, to define the rate of deterioration in Alzheimer's disease, with a view to improving clinical trials, could not be accomplished by any single organization or sector. The Allen Institute for Brain Science's goal is to produce comprehensive sets of tools for neuroscience. It is organized more like a biotechnology company than a traditional academic research organization, with functional groups in a variety of technical disciplines (neuroscience, genomics, informatics, engineering, and computing) all working together on large-scale efforts. The projects are managed tightly, with predetermined milestones and deliverables and with a core mission to create data and tools that are useful to as many researchers as possible. The Allen Institute adheres to a culture of free and open sharing of data, tools, and reagents.

Over the past eight years, the Institute has generated gene expression atlases of the adult and developing mouse brain and spinal cord and the adult and developing human and non-human primate brain. Moving forward, it will develop a connectional atlas of the mouse brain. As a result, mapping the expression of a newly discovered gene that might have required two years for an enterprising graduate student can now be done in a matter of minutes in mouse, monkey, and human brains. While there are many different organizational experiments under way, common features of successful models include a commitment to bridging multiple disciplines and to rigorous policies of open data sharing.

These examples are not meant to imply any fault with traditional academic laboratories engaged in hypothesis-driven science, but rather to point to the emergence of a new, richer ecosystem in which academic labs are enhanced by collaborations with nontraditional research organizations, government, and industry. What is critical to the success of this still-developing ecosystem will be reduced obstacles to collaboration and wide sharing of both data and reagents. Nonetheless, obstacles, not unique to neuroscience, remain to be addressed by the community if we are to move with urgency and effectiveness to develop treatments for brain disorders. For example, we must find new ways of assigning credit to participants in collaborative research and we must find new cultural and perhaps legal approaches to unwanted barriers created by intellectual property.

Specific Opportunities and Tool-Building Goals

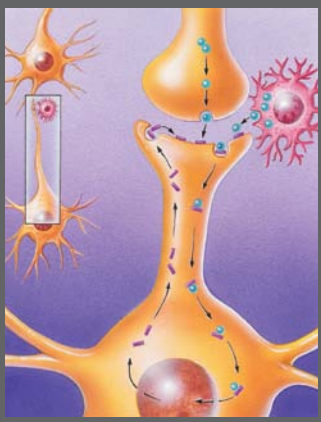
The goals described here are in more technical language than the foregoing as they are intended to initiate discussions among scientists and funders and to produce scientific proposals. Many exemplify topics that fit broadly within the shared themes described above; others extend well beyond those rubrics.

MOLECULES, CELLS, AND SYNAPSES: THE BASIC BUILDING BLOCKS OF THE NERVOUS SYSTEM

KEY OPPORTUNITIES

1. **Investigating the structure and function of key signaling and regulatory molecules within the brain.** It is now possible to obtain high-resolution structural information about critically important proteins that might be involved in brain development, information processing, adaptation to the environment, or disease pathogenesis. The application of structural, computational, and advanced imaging approaches to visualizing the structure (including dynamical aspects) of such proteins will improve the capacity to design new and better therapeutic drugs.

2. **Understanding the diversity of cell types that contribute to the formation of circuits**. As is clear from several of the shared themes stated above, it is now possible to derive comprehensive molecular, biochemical, physiological, and anatomical data on the thousands of neuronal and glial cell types that form or influence key neural circuits or that may have



SIGNALING FACTORS

Growth factors and other chemicals initiate a series of cellular events in neurons, resulting in important processes, such as neuron migration and synapse formation.

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roles in disease. Such global data sets will permit scientists to define each cell type and to identify key molecules within each type. Such information could guide the development of genetic methods, chemical probes, or therapeutic drugs to selectively influence a given cell type.

3. **Analyzing local regulation and function of protein synthesis (messenger RNA, or mRNA, translation) within neurons**. The machinery for protein synthesis exists not only within the cell bodies of neurons, but also within dendrites, the major receptive processes of neurons. This enables rapid local synthesis of new proteins in response to synaptic activity, an important adaptation in neurons, which are very large and irregularly-shaped cells. Local protein translation limits responses to those specific synapses that have been stimulated. Knowledge of the mRNAs that are translated in dendrites, their regulation, and transport to their functional sites will help illuminate many aspects of synaptic plasticity including normal learning and memory as well as diseases in which the local translational machinery is disrupted (e.g., Fragile X syndrome).

4. **Researching microRNAs as regulators of brain development and function.** MicroRNAs are small RNA molecules that regulate mRNA translation. MicroRNAs act throughout the cells, including in dendrites. Molecular genetic and computational approaches to identifying and studying microRNAs and their target mRNAs will illuminate critical mechanisms of development, synaptic function, and cell death. MicroRNAs have been implicated in several diseases, including Alzheimer's disease.

5. **Understanding membrane trafficking pathways in neurons and glia.** Membrane trafficking represents a set of processes that target proteins to the right locations within neurons. Trafficking is central to many cellular processes; significant progress has already been made in identifying and studying the proteins involved, but modern methods will accelerate progress. Some trafficking proteins have been linked to disorders including Parkinson's disease, Alzheimer's disease, and forms of autism.

6. **Determining the molecular basis of synapse formation during development.** Identifying the molecular mechanisms underlying the establishment, specification, maintenance, or elimination of synapses is a central goal of developmental neurobiology, because it will provide insight into developmental brain disorders such as schizophrenia.

7. **Identifying the molecular and cellular mechanisms of plasticity.** As the brain adapts to a constantly changing world, molecular and cellular changes take place within neurons that result in a strengthening or weakening of synaptic connections. The mechanisms involved in these adaptive changes are relevant to learning, memory, development, and thus treatment of neurodegenerative disorders and brain injury.

EXEMPLARY NEW TOOLS AND TECHNOLOGIES FOR MOLECULAR AND CELLULAR NEUROBIOLOGY

1. **High resolution *in vivo* and *in vitro* fluorescence imaging techniques.** Recent advances in fluorescence microscopy allow real-time visualization of the dynamic movements of proteins and their binding to subcellular structures in living cells. For example, multiple-color internal reflection fluorescence microscopy can track and follow the signal strength of proteins in internal membranes. Two-photon microscopy has for the first time enabled detection of changes in synaptic structure as a function of learning, behavior, or pharmacological treatment in living animals. The development of Gradient Index optics (GRIN lenses) will enable the imaging of larger populations of neurons in deeper structures of living brains. These technologies will be further advanced by the parallel development of new optical and functional probes to visualize synaptic activity, cellular metabolism, and protein trafficking and to assess spontaneous and evoked neural activity in ensembles of neurons. Particularly critical will be the development of genetically encoded and increasingly sensitive calcium and voltage sensors and other reporters of neuronal activity.

2. **Nanoscopes.** Methods have recently become available that overcome the limitations of resolution in fluorescence microscopy caused by diffraction, thus permitting astounding resolution on the order of tens of nanometers and, before long, less than ten nanometers. These methods include STORM (3D stochastic optical reconstruction microscopy); STED (stimulated emission depletion); PALM (photoactivation localization microscopy); iPALM (interferometric photoactivated localization microscopy) and TIRF (total internal reflection fluorescence microscopy). Such approaches will effectively close the gap between electron microscopy and light microscopy and offer the opportunity to perform multi-color single molecule imaging in the brain, as well as

super-high resolution reconstruction of brain structures, synapses, and neuronal assemblies. New advances will include increased speed of acquisition, ability to work on living cells, improved three-dimensional resolution, expanded multi-color imaging, and smoother interfaces with other fluorescence imaging technologies.

NEURAL CIRCUITS: THE SUBSTRATES OF INFORMATION PROCESSING AND BEHAVIOR

KEY OPPORTUNITIES

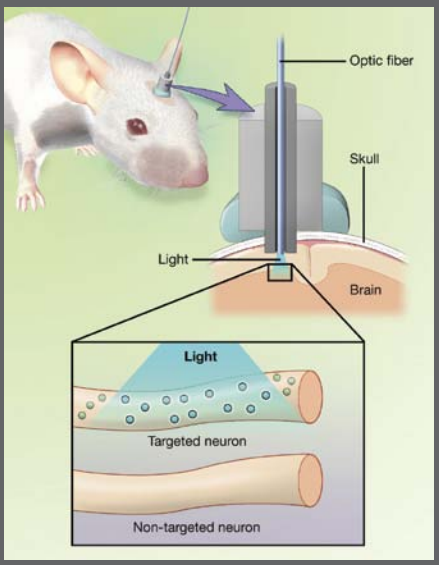
1. **Mapping small and large-scale circuits**. It will be increasingly possible to define the basic synaptic microcircuits of the brain and the larger-scale mapping of the wiring of the brain and spinal cord using new tools of the kinds described above, including light stimulation of caged neurotransmitters, light-gated channels (channel proteins that admit ions into cells in response to light—see *optogenetics* under tools, below); viral vectors that permit the introduction of genes of interest into cells; and the use of transgenic animals.

2. **Visualizing large-scale circuit dynamics**. Using new optical tools, high resolution MRI, and tools now being developed, researchers will be able to visualize the larger-scale dynamics of neuronal circuits, including both spontaneous and stimulus-evoked neural activity.

3. **Mapping the diversity of human connectomes**. As with the human genome, human wiring diagrams will be central to understanding the enormous variation in human brain function in health and disease. The 1000 Functional Connectomes Project was an early proof of concept effort that demonstrated the feasibility of combining data across sites, but the continued evolution of noninvasive human neuroimaging tools, longitudinal study designs (to permit mapping of the changing connectome over the lifespan), and efficient methods of phenotyping will have to be developed. These tools are under development through the NIH Neuroscience Blueprint: (http://www.neurosciencebluprint.nih.gov/blueprint_basics/about_bp.htm).

4. **Developing brain circuitry**. Precise connections between the 100 billion cells in the nervous system are initiated during development.

These connections are critical for proper communication and wiring in the brain but are not fully understood. Molecules such as ephrins, semaphorins, growth factors, and neurotransmitters, involved in guiding neural processes of development, dictate specific cell-cell connectivity. Defining the full complement of guidance molecules and their modification by developmental events and environmental signals represents a critical opportunity. There are vast implications for understanding a variety of neurodevelopmental disorders, as well as implications for rewiring the nervous system after injury or neurodegeneration.



OPTOGENETICS

In research using light-activated channels in genetically-modified mice, an optical fiber delivers light to targeted disease neurons in a specific brain region to restore normal function. While not ready for testing in humans, this technology has the potential to improve the treatment of many brain disorders.

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5. **Repairing brain circuits.** After injury to the brain and spinal cord, regeneration in the human nervous system is extremely limited, if it occurs at all. Molecules in the extracellular matrix and in myelin strongly inhibit regeneration. It is beginning to be possible to enhance connectivity, and more importantly, functional recovery after injury. Progress will require multiple approaches including cell transplants, antibodies, guidance molecules, chondroitinase, and growth factors. Neural plasticity and recovery of locomotion after injury should prove feasible once the inhibitory environment is relieved and rehabilitative locomotor training takes place.

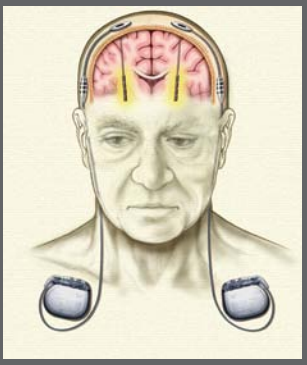
NEW TOOLS AND TECHNOLOGIES FOR THE STUDY OF CIRCUITS

1. **Transneuronally transported tracers.** Researchers are developing new retrograde and anterograde tracers that can cross multiple synapses. Researchers are also developing viral vectors that target specific cell types across species (mouse, rat, primate) by generating cell-specific promoters or by using viruses with altered envelope proteins that target cell-surface proteins.

2. **Functional implants.** Researchers have developed chronic microelectrode implants for recording neural and mechanical events. Electrical stimulation can promote axon growth and restore fine motor function. Wireless stimulating devices can facilitate chronic stimulation of sensory-motor pathways and model neuromuscular systems to address the impact of interventions and injuries.

3. **Optogenetics.** A major innovation is the ability to test whether activity in specific neurons is sufficient to elicit behavior. The use of light-sensitive ion channels, such as channelrhodopsin-2 (ChR2), has proven to be a versatile way to trigger firing of action potentials in response to light. Optogenetics has already confirmed the roles of circuits relevant to normal behaviors and illness, such as circuits involved in fear. This burgeoning technology will help identify the cellular networks activated during decision making, as well as during the learning of behavioral tasks, and in pathological states like addiction.

4. **Brain stimulation.** These are techniques for regulating neuronal activity in humans. These include magnetic and electrical stimulation devices



DEEP BRAIN STIMULATION

To help treat chronic diseases such as Parkinson's and depression, clinicians can implant electrodes deep into a patient's brain. Research indicates that electric or magnetic impulses help improve quality of life.

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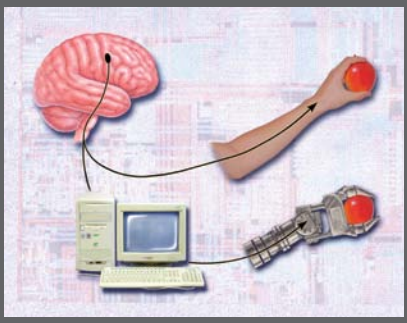
either outside the skull or, in the case of deep brain stimulation, implanted within the brain. Such technologies permit modulation of the physiological states of neural networks. These tools, used for treatment, will at the same time permit the probing of circuit function in disease and could build on current treatments for movement disorders, depression, obsessive-compulsive disorder, and many other conditions.

5. **Brain-machine interfaces (BMIs).** These are devices intended to restore sensation in the case of some forms of blindness or deafness, or motor outputs in the case of a wide range of motor deficits. BMIs are designed by recording relevant neural activity, decoding it, and then using the information to stimulate sensory regions of the brain in response to appropriate inputs or to control a prosthesis or a separate robotic limb. Advances will come from progress in imaging, signal processing, decoding algorithms, and the hardware brain interfaces themselves. The therapeutic implications are enormous both for veterans and in civilian life.

6. **Computer engineering tailored to biological problems.** New kinds of computers are being developed to simulate the behavior of neural networks within the brain. Large-scale, realistic simulations of neural networks are expected to exceed the size, speed, and parallel processing capabilities of the human brain by 2020.

7. **The neuro-observatory.** This is an audacious proposal for a real-time, high-resolution, non-invasive "scope" into cortical and subcortical activity that could provide the first view into network dynamics and will permit manipulation of circuits in the human brain. This technology, based on next-generation neurophysiology and built on the power of optogenetics, will do for human neuroscience what the recent



BRAIN MACHINE INTERFACES

Signals from nerve cells in the brain's motor cortex can control a prosthetic device. Electrical communications between neurons are recorded, processed through a machine interface, and used to control a motorized arm.

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generation of telescopes has done for astronomy. The neuro-observatory will provide the first comprehensive high-resolution picture of brain development, brain function in normal and abnormal states, and brain evolution. This project will need to be defined within specific parameters (regarding temporal and spatial resolution), as was done with the Hubble space telescope.

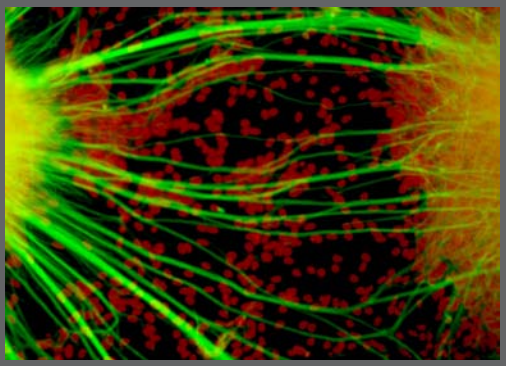
DEVELOPMENT, PLASTICITY, AND REPAIR

KEY OPPORTUNITIES

1. **Identifying the origins of neurons and glia.** Nervous system cells are derived from stem cells that have undergone a program of cell proliferation, migration, and differentiation. The exact transcriptional requirements necessary to generate different classes of neurons and glia have not been determined. The identification of transcription factors, epigenetic modifications, and the like that determine stem cells' differentiation to specific neurons and glia will be possible in the future. The resulting information can be applied, *inter alia*, to stem cells, neurons, and glial cells to facilitate repair and regeneration.

2. **Understanding critical periods.** During maturation, systems such as the visual and the auditory systems undergo transient periods of intensely changing synaptic connectivity that result in significant and permanent changes in neural circuits. These periods during development are regarded as critical periods and were once thought to produce unalterable change. However, recent data indicate that there is flexibility in the timing of the critical period that forms the adult visual system. New experiments suggest that the adult nervous system may not necessarily be as hardwired as once thought, and that it will be possible to find drugs to enhance plasticity in many systems. These basic studies will be particularly relevant to interventions for dyslexia, disorders of language acquisition, and conditions of impaired sensory integration.

3. **Facilitating adult neurogenesis.** The adult mammalian brain is capable of neurogenesis in two regions, the hippocampus and the subventricular zone. The *in vivo* potential of adult stem cells in the brain and ways to manipulate them offer possible mechanisms to treat diverse illnesses ranging from memory disorders to mood disorders.



Adult neurogenesis in the hippocampus. Green cell derived from adult neural stem cells.

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BEHAVIORAL, COGNITIVE, AND SYSTEMS NEUROSCIENCE

KEY OPPORTUNITIES

1. **Discovering the molecular mechanisms of memory.** One of the greatest challenges in modern neuroscience is to achieve an understanding of how the brain acquires, stores, and retrieves information. Extraordinary progress has been made: For example, we have learned that memory formation involves the activation of certain genes, which translates into proteins, some locally within dendrites, that can alter the fine structure of synapses, enabling specific memories to be stored at a structural level. A major challenge is to build on this progress with a view to both deep understanding of the mechanisms of memory and development of effective therapies both to prevent and treat memory loss, as it occurs in many neurodegenerative disorders, and also disorders of pathological memory such as post-traumatic stress disorder.

2. **Studying the neurobiology of language**. Language is a quintessentially human trait that is influenced by a variety of genetic factors. The first human gene implicated in speech and language disorders, FoxP2, has been discovered; further identification of vocal communication genes will facilitate a better understanding of the causes of language impairments and the biological pathways that underlie normal language acquisition. Recently it became possible to record patterns of ultrasonic vocalizations in mice. The availability of mouse genetic models, combined with progress in human genetics, should contribute to greater

understanding of mechanisms underlying developmental disorders ranging from speech sound disorders to autism. Additional insights will come from investigations of neural circuitry in humans, using neuroimaging, and in diverse animal models.

3. **Understanding the neurobiology of attention.** Attention refers to a set of higher-order cognitive processes that control the flow of information in the brain and thus the ability of humans to focus, to attend to goals and to ignore distractions (while retaining the ability to respond to emergencies). These processes are highly distributed within the brain, thus developmental abnormalities or localized damage, can impair a single aspect of attention, or can produce significant impairments of a person's ability to function in everyday life. There is now an opportunity to integrate the piecemeal understandings we have gained into a more coherent set of explanations. A deeper understanding of attentional systems will contribute to better diagnosis and treatment of a range of brain diseases, ranging from symptoms of some strokes to attention deficit disorder and depression.

4. **Investigating executive function and decision making**. Executive function is the aggregate of processes that control and integrate cognitive functions such as attention, as well as aspects of emotion and motivation. Central to executive function is the ability to hold information "on line" (in working memory) in order to coordinate diverse inputs (such as competing stimuli or a clash between goals and salient stimuli that might induce impulsive action). Executive function permits us to handle novelty and salience, choose among alternative strategies, inhibit incorrect or impulsive actions, evaluate past performance, and adjust future actions based on that feedback. Although key nodes involved in executive function are localized in the prefrontal cerebral cortex, the overall circuitry is highly distributed, as is the case for attention. Thus, executive function can become impaired within a single cognitive domain or in multiple domains, as a result of injuries, e.g., traumatic brain injury (TBI), or disease. Studies combining cognitive neuroscience with rapidly advancing neuroimaging technologies in humans, and with invasive neurophysiology in animal models promise significant progress with implications for the range of brain disorders that impair executive function, including attention deficit hyperactivity disorder, schizophrenia, dementias and TBI.

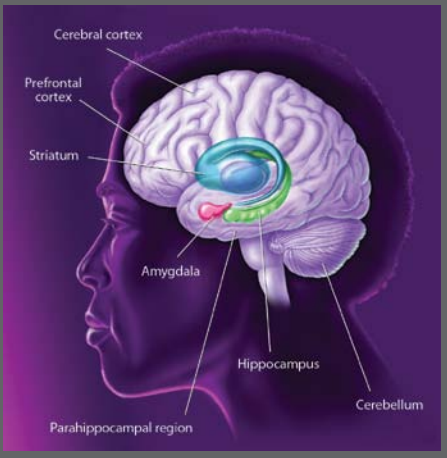
5. **Researching the neurobiology of reward and addiction.** Natural rewards, such as food, water, safety, and mating cause a person (or animal) to spend time, energy or effort, to obtain them in the service of survival of self or species. Midbrain dopamine neurons that project to the forebrain assign value and salience to rewards. Powerful evolutionary pressures have shaped the brain reward system to prioritize survival and reproduction of the species over other goals. However, the very power of the brain reward circuitry to set goals and control behavior makes us vulnerable to chemicals and to experiences that produce abnormally robust dopamine signaling in the forebrain. All addictive drugs directly cause dopamine release even though they lack survival value. Although dopamine signaling is crucial for selecting adaptive, motivated behavior, the pathologic dopamine neurotransmission induced by addictive drugs facilitates the impulsive and maladaptive behaviors that characterize substance use disorders (SUDs). A sustained and multidisciplinary research effort is critical to improving our understanding of the human reward system, its vulnerabilities, how it becomes dysfunctional in addicted individuals, and what the best strategies are for reversing some of the most devastating changes triggered by the chronic abuse of addictive substances and other rewarding behaviors that can become compulsive, such as gambling.

6. **Advancing understanding of behavioral economics**. Decision making results from complex brain processes whereby prior assumptions, current evidence, and intrinsic or perceived value are input into a computation *supposed* to generate an optimized goal-directed behavior. However, we are learning that, in reality, the process is powerfully influenced by heuristic shortcuts, biased assumptions, negative affect, beliefs, and past experience. In recent years, there has been a dramatic rise in researchers' use of behavioral economic probes (behavioral games), in an effort to characterize the way that humans value the world and make decisions based on those valuations. These efforts are not merely curiosities employed by academicians, but instead hold promise of a new approach to normal human irrationality and to the diagnosis and treatment of some mental disorders.

7. **Advancing research into fear, anxiety and fear-related memories**. We cherish some memories, but others are debilitating. Research on fear has elaborated how painful memories are acquired and made

to persist through molecular changes in synaptic transmission in the amygdala. Fully consolidated memories can be weakened by extinction, after which activation of the memory has no adverse consequences, and research is showing how synaptic changes in the amygdala and prefrontal cortex contribute to this process. Consolidated memories can also be altered (weakened or strengthened) by an infusion of drugs into the amygdala that prevents the reconsolidation of the memory after retrieval. Combining extinction with reconsolidation (i.e., using extinction instead of a drug after reactivation of the memory) appears to be even more effective. Recent research using viral manipulations of brain molecules has led to significant advances. For example, studies using viruses to alter neurotransmitter trafficking or to optically activate and inactivate neurons have given researchers new insights into fear learning mechanisms. Work on fear has important implications for fear- and anxiety-related disorders in humans. Particularly important for the future will be more detailed analysis of the biological mechanisms that account for individual differences in fear learning and memory, since these might reveal what predisposes some people to develop fear disorders.

8. **Understanding affiliation and pair bonding**. Over the past decade there has been remarkable progress in our understanding of the neurobiological mechanisms underlying complex social behaviors, including social recognition, affiliation, and social attachment. Studies of the socially monogamous prairie vole, for example, have highlighted the roles of oxytocin, vasopressin, and dopamine systems in promoting



MEMORY

Memories, from simple recollections to fearful experiences, are supported by a variety of brain structures, including the hippocampus, amygdala, and striatum.

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social bonds between mates, or pair bonds. Comparative studies using both monogamous and asocial, polygamous voles have revealed that variation in the expression patterns of oxytocin and vasopressin receptors in the brain are associated with variation in affiliative behaviors, both between species and among individuals of the same species. Studies examining the effects of early-life maternal nurturing on later life parental behavior and brain neurochemistry in rats have demonstrated that developmental social experience can shape adult social behavior and oxytocin receptor expression in the brain through epigenetic mechanisms. Perhaps the most intriguing aspect of this new social neuroscience field is the discovery of remarkable parallels in the roles of oxytocin and vasopressin systems in regulating aspects of human social relations. Dozens of studies over the past few years have shown that in human subjects, intranasal oxytocin increases trust, the ability to infer the emotions of others, and empathy, and that it enhances socially reinforced learning. This conservation in the neural mechanisms regulating rodent social bonding and human social cognition significantly enhances the translational opportunities in this field. For example, intranasal oxytocin enhances some aspects of social functioning in human subjects. Findings from research on social bonding in voles may be extrapolated for use in screening drugs to enhance social cognition, which in turn may be useful in treating psychiatric disorders with social deficits. The combination of genetic analysis, pharmacology, and brain imaging in human subjects promises to provide an even better understanding of the gene, neurochemistry, and neural circuitry interactions involved in living in a social world. Such studies have implications not only for autism spectrum disorders and the social deficits of schizophrenia, but also for important, but poorly understood, disorders such as dissocial personality disorders.

9. **Tracing the pathways linking chemosensory perception to emotion.** To ensure their survival and transmission of their genes, animals must recognize the key features of their environment, identify food sources, avoid predators or other dangers, identify members of their own species, and engage in fruitful social interactions. In many species, the perception of the environment and the recognition of other individuals within the animal group rely on the detection of olfactory and pheromone signals that, in turn, activate neural circuits underlying adaptive behaviors and emotional responses. The discovery

of odorant and pheromone receptor genes in the early nineties has led to remarkable breakthroughs in our understanding of how the brain encodes olfactory signals by providing exquisite molecular and genetic tools to start deciphering the sensory processing of dedicated behavioral neural circuits. Although humans are likely to use mainly non-olfactory sensory cues to detect social and stressful stimuli, the central coding and processing of cues leading to appropriate social or defensive responses—for example, the ability to solve conflicting social cues, often impaired in mental illnesses—is likely to be similar. Thus, neural principles uncovered in animal studies are applicable to human health and diseases, and may help guide diagnostics and therapy.

10. **Shedding light on the role of circadian rhythms in health and disease**. An autonomous master clock, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, controls circadian behavior in mammals. The SCN is sensitive to environmental changes in the light/dark cycle,

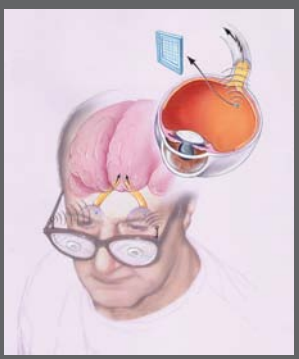
GENE THERAPY

In three independent early-phase clinical trials, human gene therapy has restored partial vision to children with an advanced form of Leber congenital amaurosis (LCA), a severe congenital retinal degenerative disease. These landmark clinical trials have paved the way for applying gene therapy to a host of retinal diseases. In November 2010, the Food and Drug Administration granted approval to begin clinical trials of a novel gene therapy to prevent catastrophic vision loss from age-related macular degeneration (AMD), the most common cause of blindness in older Americans. Recent laboratory studies of common diseases such as AMD, glaucoma, uveitis, and several rare but severe diseases have demonstrated proof of concept that gene therapy offers therapeutic benefit for some conditions. These positive findings are now allowing investigators to pursue the pre-clinical work necessary to gain regulatory approval for conducting clinical trials. Those in the eye and vision research field are optimistic that gene therapy could one day become an invaluable treatment for vision loss, and might restore sight for a variety of neurodegenerative eye diseases.

THE RETINAL PROSTHESIS ENTERS CLINICAL TRIALS

NIH investigators are developing prosthetic devices to function in place of neurons lost to disease. Retinal degenerative diseases such as retinitis pigmentosa and AMD destroy the light-sensitive photoreceptor cells in the retina. Although these cells die, much of the remaining nerve cell network in the retina remains healthy. Implanted retinal prosthetic devices replace photoreceptor function by electrically stimulating the remaining retinal circuitry to encode visual information. With considerable support from NIH, a company called Second Sight has developed the Argus II retinal prosthesis. In clinical trials of the Argus II, patients were able to perceive changes in light level, locate objects in the visual field, walk along straight lines, and detect motion. The Argus II is just one of several prostheses being developed with NIH support. With further refinement, these devices could greatly improve independence, mobility, and quality of life for those who are blind from retinal diseases.

and synchronizes a multitude of peripheral clocks present in almost all tissues. Each individual cell harbors a molecular clock composed of a set of proteins that oscillate in a circadian fashion. While different cell and tissue types can vary in their response to synchronization cues, the composition and function of the core molecules that constitute the intracellular clock are conserved. Sleep disorders are prevalent in the United States, with nearly 70 million cases annually, costing $100 billion.



VISUAL PROSTHESIS

In diseases such as age-related macular degeneration, the light-sensing photoreceptor cells of the eye are destroyed; however, many of the other cells in the visual pathway remain functional. Implantation of a prosthetic retina can electrically signal the remaining retinal circuitry to encode visual information to the brain.

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Problems with sleep present in many different ways, including memory deficits and increased risk of depression and alcohol and drug abuse. Persistent sleep problems in children are also related to higher rates of obesity and anxiety disorders later in life. However, the majority of cases are undiagnosed and untreated.

11. **Exploring the neurobiology of stress**. Stress is a major problem across the globe. The brain is the key organ in the response to stress because it determines what is threatening and, therefore, potentially stressful, as well as the physiological and behavioral responses of the body, which can be either adaptive or damaging. Too much stress can promote diseases such as depression and cardiovascular disease, and traumatic stress can lead to post-traumatic stress disorder. Stress involves two-way communication between the brain and the metabolic, cardiovascular, immune, and other systems via neural and endocrine mechanisms. Beyond the "flight-or-fight" response to acute stress, the amount of perceived stress, as well as circadian disruption brought about by such things as jet lag and shift work, can lead to such detrimental behaviors as poor sleep, unhealthy diet, lack of exercise, smoking, and excessive alcohol consumption, all of which add to the physiological load on the body and brain. The effects of stress upon the brain can occur *in utero* and in early postnatal life, and can have lasting effects on brain development, behavior, and the operation of the stress-response system. Critical goals include investigation of individual susceptibility to stress including both genetic and epigenetic risk factors, and the development of both preventive interventions and treatments for stress-related disorders.

TOOLS AND TECHNOLOGIES TO ADVANCE BEHAVIORAL AND COGNITIVE NEUROSCIENCE

1. **Advances in neuroimaging technologies**. In the past thirty years, there has been an explosion in technology that allows us to look inside the human brain. These imaging modalities let us "look" at the gross anatomy of the brain using CAT scans and structural MRI. Positron emission tomography (PET) and SPECT utilize radiochemical ligands to determine the distribution of receptor densities and other clinically and physiologically relevant compounds, including the distribution of amyloid protein in Alzheimer's disease. The development of ligands that

can image new compounds, and can do it in better ways, is an exciting and burgeoning area of research. An MRI technique, diffusion imaging, can be used to explore white matter pathways that anatomically connect different parts of the brain to each other. Other large-scale imaging methods, most notably functional MRI but also optical imaging, MEG/EEG, and PET, can be used to measure the activity of neuronal populations with resolutions in the multi-millimeter range. Each of the methods has its own trade-offs, in terms of spatial and temporal resolution and signal strength. The process of building combinations of anatomical and physiological imaging techniques to address complicated neurobiological questions is beginning to pay off now, and offers incredible promise for the future. Recognizing this promise, many institutions are taking part in the NIH-sponsored Human Connectome Project, which aims to eventually provide a large database of anatomical and physiological imaging, genetic, and behavioral and phenotypic data on a large population. (See shared theme: The Connectome)

2. **Predictive algorithms in neuroimaging**. In recent years, functional neuroimaging has provided important insights into how the healthy brain works and into how it is impaired in states of disease. These images are large data sets, the analysis of which must be predicated on the application of cutting-edge signal processing algorithms and statistical methods to ensure that the most appropriate inferences are drawn. At present, data accrue from these studies at rates that far exceed the rate at which new methods are available with which to analyze them appropriately. Therefore, the development of statistical methods for functional neuroimaging must continue to be an active area of neuroscience research. The statistical techniques developed in bioinformatics research were a vital part of the genomics revolution in the last part of the 20th century; similarly, development of statistical methods for functional imaging and for neuroscience research in general must be a vital part of the neuroscience revolution in the 21st century.

NEUROBIOLOGY OF DISEASE

The neurobiology of disease is a branch of basic, rather than clinical, neuroscience, as it focuses on the molecular, cellular, synaptic, and circuit-based mechanisms of disease rather than on clinical treatment development, clinical trials, or important descriptive research, such as

epidemiology, regarding human populations. This field is a critical platform from which much of translational neuroscience takes off.

KEY OPPORTUNITIES

1. **Visual system: Developing therapies for neurodegenerative eye diseases.** Advances in genetics, brain machine interfaces, and stem cells have all produced exciting clinical applications for neurodegenerative diseases of the eye.

STEM CELLS IN EYE DISEASE

Stem cells have many promising applications in the prevention of vision loss and the restoration of sight due to injury or disease. Already, the FDA has granted approval to begin clinical trials using retinal pigment epithelial (RPE) cells derived from human embryonic stem cells (hESCs) to treat AMD and Stargardt macular dystrophy. The RPE is a layer of cells adjoining the neural retina that supports photoreceptor cell function. In both AMD and Stargardt disease, RPE cells degenerate and die, which leads to the death of photoreceptors and vision loss. In these clinical trials, investigators will inject RPE cells to replace those lost to disease. This approach has prevented disease progression and vision loss in a rodent model of Stargardt disease. In a similar study, investigators have prevented disease progression in a rodent model of RPE cell degeneration using RPE cells developed from human-induced pluripotent stem cells (iPSCs). iPSCs are derived from adult cells that have been reprogrammed to lose their tissue-specific properties, allowing them to differentiate into any cell type. In still other studies, bone marrow–derived stem cells stabilized abnormal blood vessel growth in animal models. This approach is thought to have utility in treating ischemic diseases, such as retinopathy of prematurity or diabetic retinopathy, in which abnormal, leaky blood vessels damage the retina. While there is still much work to be done, stem cells represent a rare opportunity to restore vision to patients with a variety of eye diseases.

2. **Researching the auditory system.** Damage to the exquisitely sensitive sensory hair cells of the inner ear can have a devastating effect on daily life, by causing either hearing loss or loss of balance. While many tissues and organs have regenerative capacity, for the sensory hair cells within the mammalian inner ear, this capacity, once lost, is irreplaceable. Because of the highly specialized functions of the inner ear, its inaccessibility, and its variety of cell types, therapies for hearing/balance impairment have been extremely challenging to develop. Today, artificial devices such as hearing aids—which require some functional hair cells—and cochlear prostheses are used to treat hearing loss. Recent animal studies have established the feasibility of using small electrical pulses to restore aspects of balance after a profound loss of hair cells; the technology needed for such a device exists in the cochlear implant. While continued improvement in the technology and performance of the artificial prosthesis is critical, the value of regenerative therapies would be enormous. Mouse ESCs and iPSCs can become viable hair cell candidates with measurable mechanosensory function *in vitro*. Transplantation procedures and cell replacement strategies are still in their infancy, but advances in stem cell research are a critical first step toward novel human hearing/balance therapies.

3. **Examining the synapse as a common site for disparate diseases.** Knowledge gained from basic neurobiology on cognition, learning, and memory is being applied to our understanding of many neurological and psychiatric diseases. It is clear that there is a convergence of multiple disease mechanisms on synaptic signaling cascades whose normal function is important for brain development and synaptic plasticity. Importantly, recent research has shown that disease can result from dysregulation of the same processes that increase and decrease synaptic strength for normal behavior, namely long-term potentiation (LTP) and long-term depression (LTD). Alterations in the initial formation of synapses in the developing brain can result in autism and intellectual disability. Abnormal connectivity is thought to contribute to schizophrenia. Enhanced activity of excitatory synapses results in epilepsy, and extreme overactivation contributes to cell death in stroke and brain trauma (excitoxicity). Addiction has been shown to involve a pathologic form of learning at synapses in nucleus accumbens and other prefrontal structures, leading to compulsive drug-seeking behavior. Likewise, chronic pain can result from abnormal synaptic strengthening

in the dorsal horn of the spinal cord. As a result of this research, the synapse, including the post-synaptic density (PSD) and its proteome, are now being researched as potential drug targets for diverse disorders, e.g., chronic pain, autism, obsessive-compulsive disorder, epilepsy, addiction, depression, and schizophrenia.

4. **Studying channelopathies as a source of neurological disease**. Over the past two decades, there has been an increasing awareness of the fact that previously unrelated diseases are actually related because they involve a dysregulation of ion channels. Ion channels regulate normal excitability in neurons and skeletal muscle, and derangement of their function can result in disorders including periodic paralyses, epilepsy, and migraine. In all instances, the knowledge that the neurobiological cause is a channelopathy has guided development of treatments. For instance, many antiepileptic medications block sodium channel activation or activation of neurotransmitter receptor-mediated ion channels. Migraine is one of the most common neurological disorders, affecting more than 30% of the population, and calcium channel blockers can attenuate headaches. Knowledge of specific ion channel mutations in hereditary myotonias and periodic paralyses is being applied to the development of new ion-modulating treatment strategies. While channelopathies mediate the expression of these disorders, they are also likely to be influenced by other genetic and non-genetic factors. The complementary disciplines of molecular genetics and cellular and *in vitro* electrophysiology will continue to join forces to seek significant advances in understanding of the basic molecular pathophysiology of these disorders and to develop more effective treatments.

5. **Redefining neuropsychiatric disease for the twenty-first century.** An exciting process of redefining neuropsychiatric disease is taking place based on advances in neuroscience and genetics. Molecular, cellular, and neural circuit-based research is revealing similarities among diseases that were never before thought to be related, and enabling wider application of newly discovered treatments and diagnostic tests. In the past, many treatments for neuropsychiatric ailments were largely symptomatic therapies, but now the emphasis is on unraveling the steps involved in disease initiation and progression, in order to develop treatments that are truly "disease modifying." Neurobiological research is in the midst of a revolution that will make it increasingly possible to

AN EXAMPLE: PROPOSED QUANTIFIABLE GOALS FOR SCHIZOPHRENIA

Step 1: Genome-wide association studies (GWAS) have already identified approximately fifteen strong and replicated loci associated with risk of schizophrenia. Analysis of 10,000 schizophrenia cases strongly suggests that many new loci could be discovered if the sample size were increased to 50,000 cases and 50,000 controls. It is feasible to attain such numbers by 2012, based on existing collaborations and genotyping with a commercially available chip. Such an effort would not compete with sequencing projects to follow (steps 2 and 3), and could make a distinct contribution to the identification of rare variants associated with disease. Success would galvanize neurobiology. *Step 2: Whole exome sequencing of the 10,000 patient samples already available*. One sample collection already contains a number of trios: an affected child and two healthy parents. *Step 3: Whole genome sequencing.* The exact design of step 3 would depend on the findings of steps 1 and 2. Steps 2 and 3 area feasible based on the falling cost of sequencing**.**

For schizophrenia, current data indicate that copy number variants, some de novo and some inherited, play an important role in etiology risk. This is most easily assessed in trios consisting of two unaffected parents and an affected child. Thus, whole exome and whole genome sequencing should also be performed on at least 2,000 trios (6,000 samples) to search for *de novo* point mutations and smaller deletions or other smaller copy number variants. If this plan is followed for schizophrenia and bipolar illness and replicated for autism, the field will be in a far better position to discover the abnormal neurobiology, create screens for new drugs, develop better animal models, and be on a new trajectory toward better diagnoses and treatments. In addition, it is likely that knowing the full scope of genetics risks, one could begin to plan early intervention studies in a rational way.

diagnose disease before it becomes manifest, as well as to interrupt disease before it progresses.

6. **Researching developmentally specific disease manifestations and their implications for treatment.** It is clear that the developing brain of an infant, child, or even adolescent is not simply a smaller version of an adult brain. Of all the organs in the body, the brain is the last to reach full maturity; this does not occur until well into the third decade of life. Diseases that exemplify the impact of these differences in brain maturity across the lifespan include premature brain injury, epilepsy in infants and children, and adolescent mental illness and addiction. Vulnerability to injury appears to depend upon the regional maturation of the brain: when subcortical and white matter areas are affected in premature infants, it can lead to cerebral palsy, and when grey matter in the basal ganglia and cerebral cortex is affected in the injured term infant, it can lead to seizures and cortical strokes (while white matter is relatively unaffected). It will be necessary for researchers to extend current functional MRI imaging, as well as work on epigenetic and molecular mechanisms of physical or psychological early-life trauma, to shed light on the trajectory of brain development and risk profiles for subsequent neuropsychiatric disability. Recent longitudinal MRI imaging studies on people with childhood-onset schizophrenia and on those with ADHD have revealed abnormalities in cortical development. Well-characterized cohorts can lead, *inter alia*, to better understanding of symptoms, pathogenesis, and the timing of disease-altering therapies as they become available.

Epilepsy is a common neurologic disorder that is highly prevalent in the developing brain. Epilepsy syndromes are largely age-dependent, and include neonatal seizures, infantile spasms in the first eighteen months of life, childhood absence epilepsy (formerly known as *petit mal*) in the elementary school years, childhood rolandic epilepsy in children and preadolescents, and juvenile myoclonic epilepsy in periadolescence. Each of these syndromes involves different neuronal circuits that are transiently susceptible to hyperexcitability. New research has led to treatment strategies that are based on the unique physiology of the afflicted age group. As there is not yet a cure for epilepsy,

experimental and translational studies are required to understand the often age-dependent molecular cascades that trigger it.

Mental illness is also highly age-dependent. Research on normal brain development is improving our understanding of why major affective disorders like schizophrenia first become symptomatic in the late postadolescent and young adult years. Neurochemical differences in teenagers, when compared to adults, have been identified as a reason for their different responses to antidepressant medication. Functional MRI imaging has shown that the process of myelination that enhances inter-regional connectivity is ongoing, not becoming complete until the mid-twenties. Importantly, the last area to become fully connected is the frontal lobes, which are involved in insight, judgment, and impulse control; this relative lack of connectivity has been thought to contribute to the increased risk-taking behavior characteristic of teenagers. In addition, recent cellular and molecular studies have shown that teenagers may be more susceptible to addiction to psychotropic drugs, given that they are still within a critical period of heightened synaptic plasticity. Research on brain development will continue to have important societal, as well as medical, implications.

Studying the neurobiology of autism and related disorders. Over the past decade autism has gone from being a mystery to a tractable, if still difficult, focus of scientific efforts. Genes for several disorders with features of autism (Fragile X, West's, Rett's, tuberous sclerosis, Angelman syndrome) have been identified. Subsequent identification of proteins encoded for by these genes is revealing that many of the affected genes map to important elements involved in early synapse formation in the brain and those involved in learning and memory. Rapid advances are now occurring as scientists apply these findings to genetically engineered mice that possess these mutations for the purpose of finding therapeutic targets. In the past five years, several major pathways have been shown to have potential for modifying the development deficits. Currently, early phase clinical studies with drug therapies are directed at new targets, and this will be a major area of future translation.

7. **Using modern genetics to probe the biology of neuropsychiatric diseases.** Autism, schizophrenia, and bipolar disorder are among the most strongly genetically influenced of all common genetically complex disorders in medicine. Thus, the identification of risk genes could provide valuable clues for identifying molecular mechanisms of pathogenesis for these devastating disorders. In turn, such discoveries could lead to molecular targets for much-needed new treatments. The combination of genetic complexity and the lack of objective phenotypic tests have proved major impediments to progress, but in recent years application of advanced genomic technologies to large patient samples has yielded significant advances for the first time. In schizophrenia and autism, both common sequence polymorphisms and copy number variants (CNV) have been shown to contribute to risk, and in bipolar disorder, common variants have been identified—indeed, a lack of excess CNV may partly distinguish bipolar disorder from schizophrenia. These genetic findings are already stimulating exciting efforts to understand the neurobiology of these diseases. It is both timely and crucial to apply modern genetic technologies to these and other neuropsychiatric disorders in order to identify, with certainty, molecular pathways that are involved in the pathogenesis of these disorders. Because of the large aggregate effects of genes, the severity of the disorders, and the existing patient samples and DNA collections, autism, schizophrenia, and bipolar disorder should represent the initial goals of these efforts.

8. **Exploiting the genetics of neurodegenerative diseases and dementia.** Genetics has played a crucial role in identifying molecules that are becoming key therapeutic targets. Research in humans identifying these pathways has led to the development of experimental models in which treatments can be developed. Alzheimer's disease is the most common form of dementia in the elderly. There are two major forms: the first is characterized by strong Mendelian familial clustering and an early onset, and the second is characterized by a later-onset age (beyond 65 years), without familial aggregation. The vast majority of Alzheimer's is the second form, late onset, which is likely to be governed by an array of low penetrance common risk alleles across many loci. Emerging genomic technologies will be necessary to identify the causes of the more common Alzheimer dementia types, which will not only allow for better prediction and diagnosis but will also yield new target therapies.

9. **Using the molecular mechanisms of neurodegenerative disorders to lead the way to new therapeutic strategies.** Some of the most devastating conditions to affect humans are the neurodegenerative diseases. Examples include Huntington's disease, Alzheimer's disease, Parkinson's disease, ALS, and prion-related diseases. Parkinson's disease is one of the most frequent neurodegenerative disorders; research in the twentieth century revealed that the motor symptoms were related to a loss of dopaminergic neurons, mainly, but not exclusively, in the substantia nigra pars compacta (SNpc). More recently, the dementia that can accompany the movement disorder has been shown to result from cortical degeneration, including Lewy bodies, as well as Alzheimer's-like pathology. While current treatments address the neurochemical deficits that result from dopaminergic cell loss, ongoing research is evaluating application of cellular replacement with pluripotent stem cells (iPSCs), which have the ability to differentiate and proliferate. Parkinson's is likely to be one of the disorders most amenable to stem cell therapy, as the underlying cellular and neurochemical deficits are highly characterized and can guide the development of source cells for implantation. In addition, due to improved knowledge of how cell loss impairs the balance of connectivity within the brain, deep brain stimulation (DBS) is now a reality for treatment in drug-resistant cases of the disorder. DBS is still limited by adverse effects, however, and future research will be needed to optimize the stimulation method.

10. **Uncovering the mechanisms of normal aging that may produce vulnerability to disease.** In addition to work on specific age-related disease states such as Alzheimer's dementia, much research is evaluating more general aspects of brain aging, including age-related increases in protein misfolding and abnormalities of protein degradation, susceptibility to oxidative stress, mitochondrial injury, calcium dysregulation, excitotoxicity, and synaptic loss. An important field for aging is that of epigenetics, which looks at how gene expression can be affected by environmental factors and toxins over a lifetime. Identification of these epigenetic factors will result in new preventive strategies to reduce the risk of cumulative age-related nervous system dysfunction. Another area of investigation is the potential role of stem cell–based therapies to repair damage to sensitive areas of the aging nervous system.

11. **Determining specific risk factors, pathophysiological mechanisms, and treatment approaches for chronic traumatic encephalopathy.** Chronic traumatic encephalopathy (CTE) has been linked to participation in contact sports, such as boxing and American football. It is believed that repetitive brain trauma, with or possibly without symptomatic concussion, is responsible for neurodegenerative changes highlighted by tauopathy and TDP-43 proteinopathy. Over time, CTE results in a progressive decline of memory and cognition, as well as depression, suicidal behavior, poor impulse control, aggressiveness, Parkinsonism, and, eventually, progression to dementia. In some individuals, it leads to a motor neuron disease similar to ALS, referred to as chronic traumatic encephalomyelopathy (CTEM). Recent neuropathological research has shown CTE may be widespread in former contact sport athletes. Given the millions of youth, high school, and collegiate athletes participating in contact sports involving repetitive brain trauma, as well as the thousands of troops exposed to repeated brain trauma from blast and other injuries in the military, CTE represents an important public health issue. Focused and intensive study of the pathophysiological mechanism through animal modeling, determining risk factors (including genetic), and *in vivo* diagnosis of CTE and CTEM through cerebrospinal fluid biomarkers and neuroimaging techniques will allow for the rapid investigation of methods to prevent and treat these diseases. Research will also provide policy makers with urgently needed scientific knowledge to come up with appropriate guidelines for the prevention and required treatment of brain trauma at all levels of athletic involvement, as well as in the military theater.

12. **Studying the role of the immune system and inflammation in neurological diseases.** Both innate and humoral immunity are increasingly recognized as sources of disease in the nervous system, resulting in patterns of inflammation in the brain and spinal cord that are unique when compared to other organ systems. Autoimmunity has been shown to be a key factor in multiple sclerosis (MS); research in this area is leading the field, but has important implications for other CNS immune diseases, including encephalitis. Over the past two decades, understanding of the role of the innate immune system in mediating damage to myelinated axonal tracks has led to a wealth of therapeutic targets, some of which are currently in use or in clinical trials and have proven efficacy in slowing the pace

of this often-unrelenting disease. As they are newly uncovered, treatment advances in MS are being adapted for other immune-mediated disorders, including encephalitis, transverse myelitis, and chronic inflammatory peripheral neuropathy. In some cases, immunosuppressant treatments can be completely curative, such as in the acute paralytic Guilllian Barre syndrome. Roles for inflammatory mediators are also hypothesized in depression, epilepsy, Alzheimer's disease, and ALS. Microglia may play an important role in chronic pain and other nervous system disorders; the immune system might even play a role in obsessive-compulsive disorder. Finally, components of the major histocompatibility complex (MHC) are expressed in neurons and might influence activity-dependent plasticity and neuropsychiatric disorders, such as schizophrenia, autism, and dyslexia.

TOOLS AND TECHNOLOGIES FOR THE NEUROBIOLOGY OF DISEASE

1. **Connectomics.** Only in the past decade have advances in computation methods and modeling permitted multimodal measurement of the normal and diseased human brain. Data can be merged from functional magnetic resonance imaging (fMRI), MRI diffusion tensor tractography (DTI), electroencephalography (EEG), and magnetoencephalography (MEG) to examine patterns of dysconnectivity present in different diseases and to assess how these diseases alter the activity and function of the brain *as a whole*. Information from deep brain stimulation (DBS) and rTMS can also be integrated. Important new insights are being obtained in this way, especially regarding early brain injury and neuropsychiatric disorders such as schizophrenia, epilepsy, and dementia. New biomarkers and surrogate markers can be developed for future monitoring of disease risk, progression, and treatment response. Even more importantly, connectomics is capable of elucidating disease pathology to a greater extent than any of these conventional tools in isolation. (See shared theme: The Connectome)

2. **Brain-machine interfaces for treatments based on systems neuroscience**. These include cochlear implants; artificial retina; DBS for Parkinson's disease, epilepsy, and neuropsychiatric diseases; occipital cortex stimulation for blindness; and peripheral stimulation for spinal cord paralysis.

3. **Advanced materials for invasively exploring brain function.** These will include the use of new steerable catheters for angiography, clot removal, and for recording seizure foci prior to surgery.

4. **A National Neuroscience Biobank (with support from the Department of Defense and National Institutes of Health).** For each of the central nervous system disorders, this will constitute a curated, high-quality repository of DNA, iPS cells, brains, cerebrospinal fluid, and serum linked to high-quality, standardized phenotyping. This effort will require partnership with the patient advocacy community for recruitment (and grief counseling), a network of centers trained to specific quality standards, an informatics framework, and a fair process for allocating non-renewable samples. This biobank, whose establishment can be guided, to some degree, by information gained from the recent CaHuB effort for cancer, need not be disease specific. While there should be milestones for recruitment and quality control, the biobank would be an ongoing effort to build capacity in specific areas of need, such as developmental disorders and rare Mendelian disorders.

CLINICAL NEUROSCIENCE

KEY OPPORTUNITIES

1. **Rethinking curricula to break down intellectual silos**. The historical distinctions between neurology and psychiatry—as well as clinical psychology—are beginning to break down based on new scientific discoveries and clinical observations. Patients with movement disorders may suffer significant disability and distress as a result of depression and cognitive impairments. Patients with treatment-refractory depression and obsessive-compulsive disorder may find relief from deep brain stimulation. Children with autism, attention deficit hyperactivity disorder, and learning disorders are initially treated by child neurologists, psychiatrists, or behavioral pediatricians. Ultimately, patients benefit when matched with clinicians who have the right training and deep experience with their disorder(s), rather than membership in one medical subspecialty or another. An important opportunity for improving patient care—ensuring that all aspects of a patient's brain disorder are recognized, and that the patient receives appropriate, evidence-based treatment—is through the development

of better, scientifically driven curricula for current and developing practitioners of clinical neuroscience. Such curricula should be shared not only among neurologists, psychiatrists, and psychologists, but also among neurosurgeons and neuroradiologists. These latter practitioners have specialized skills, but their fundamental understanding of the brain should overlap with that of the other specialists.

2. **Training translational neuroscientists and clinical investigators.** The steady loss of physician-scientists is one of the obstacles to the translation of basic discoveries into treatments and to the application of the best uses—including novel uses—of approved treatments. Financial support, advanced curricula, and experiential research and training opportunities will prove critical to launching such careers. An appropriate infrastructure and funding for translational neuroscience will be critical to sustaining them, and to the discovery and development of much-needed new treatments. Not to be forgotten is the rich source of basic scientists, with their interest in disease mechanisms and willingness to commit careers to pursuing the basic biology of nervous system disorders. An important goal is to establish training programs that allow these scientists to understand better the nature of disorders and to encounter patients in settings that allow them to gain a personal perspective on the manifestations of neurological and psychiatric disorders. Recruiting this source talent would hasten our understanding of disease pathogenesis and treatments.

3. **Investigating biomarkers**. Alzheimer's disease will represent an enormous cost in terms of health care dollars over the next two decades as the baby boomers reach age 65 and older. With other neurodegenerative disorders such as Parkinson's, Huntington's diseases, amyotrophic lateral sclerosis, Lewy body dementia, frontotemporal dementia, multiple system atrophy, and others added in, a real epidemic will ensue requiring large amounts of resources—unless breakthroughs in basic and clinical research provide biomarkers of disease onset and burden and lead to effective therapies. Previous sections of this plan highlighted many of the advances made in understanding and treating these diseases through basic science discovery, human genetics, detailed clinical phenotyping, and proteomic and metabolomic research. Now large-scale efforts (recent success in Alzheimer's disease is an inspiring example) are needed to develop

biomarkers for many brain disorders in order to improve the design of treatment trials and to support diagnosis. For disorders that lack any objective medical tests, such as depression and some chronic pain syndromes, the lack of biomarkers has markedly impeded treatment development. For neurodegenerative disorders in which clinical trials and treatment must likely start in presymptomatic or mildly symptomatic individuals, it is hard to imagine progress without biomarkers.

4. **Improving psychiatric diagnosis**. For many neuropsychiatric disorders, especially those described by the anachronistic misnomer of "mental illnesses," it is critical to move from the shallow descriptive diagnoses of today to objective diagnoses based on intermediate (neurobiological) phenotypes—perhaps constrained by genetic tests (the utility of which is limited, for now, by genetic complexity). The current revisions of the DSM-IV and ICD-10 should be exploited to encourage translational and clinical research that is not limited by the current disorder definitions.

5. **Developing a "Framingham Study of Brain Disorders".** There has been no longitudinal cohort for central nervous system disease except for Alzheimer's. In line with the campaign's focus on soldiers and veterans, why not launch a long-term follow-up of 100,000 eighteen-year-olds who volunteer for military service? In fact, this is being done as a five-year effort in the Army STARRS study with the Department of Defense and the National Institute of Mental Health, but it could become a forty-year study, á la Framingham, with an opportunity to look at risk and resilience throughout adulthood. The study might be improved by adding additional biomarkers, such as resting state fMRI.

6. **Identifying developmental risk factors and producing effective interventions.** Many brain disorders, such as autism, Fragile X syndrome, Rett syndrome, tuberous sclerosis, and schizophrenia have neurodevelopmental roots, whether genetic, environmental, or some combination. Recognizing and mitigating risk factors (by medical, nutritional, or societal means—as in the case of child abuse and neglect) would have major benefits. Reversing damage done by risk factors (e.g., by early treatment interventions, whether behavioral or pharmacologic) might prove to be effective form of prevention. New research on the epigenetic marks produced by stress or certain drugs provides exciting new avenues for research. When risk factors cannot

be controlled and symptoms of brain disease begin to emerge—at any point in the life span—early intervention often has special benefits. This requires improved diagnostics and new, developmentally sensitive treatments for early-onset disorders.

7. **Discovering new treatments for pain, including neuropathic pain.** Pain is associated with the release of many molecules, including neurotransmitters, bradykinin, eicosinoids and lipids, trophic factors, cytokines, and chemokines, which enhance excitability of the nerve fiber, thereby heightening its sensitivity to temperature or touch. Chronic pain may also be associated with activation of microglia. All standard treatments for pain have side effects and limitations in efficacy, such as aspirin and nonsteroidal anti-inflammatory drugs (ulcer risk and cardiovascular risk for the latter) and opiates (subject to tolerance, dependence, and addiction liability). Current treatments for neuropathic pain (e.g., anticonvulsants) also leave much to be desired. Exciting new approaches to therapeutics include blocking NGF or TNF-alpha action with neutralizing antibodies and pharmacologic approaches to inhibiting trophic factors or inflammatory mediators. In addition, Na+ channels and TRP receptors may prove to be important targets for new analgesics.

8. **Treating disorders of neural signaling and pathological synchrony**. These disorders include epilepsy, migraine, some channelopathies, and other paroxysmal disorders. Excitatory and inhibitory processes need to be precisely calibrated to ensure correct information processing; an imbalance in synaptic excitation and inhibition can lead to epilepsy and related disorders. Understanding the molecular and cellular bases of these disorders should revitalize treatment discovery.

9. **Treating disorders of immunity or inflammation**. Recent findings suggest that a number of psychiatric disorders, including major depressive disorder, bipolar disorder, and schizophrenia, are accompanied by elevations in pro-inflammatory biomarkers, and that the use of anti-inflammatory drugs may provide some benefit to patients with these conditions. Similarly, cerebral inflammation is a common phenomenon during the progression of neurodegenerative diseases. There is great interest in developing new treatments that address these inflammatory processes in neurological and psychiatric disorders.

10. **Treating metabolic and mitochondrial disorders**. Although mitochondria were first described 120 years ago, the first mitochondrial disease was only reported in 1962. Since then, more syndromes affecting numerous organ systems, including the brain, have been reported. In addition, among their other symptoms, people diagnosed with mitochondrial disease have higher-than-usual rates of neurological symptoms and psychiatric disorders such as major depressive and bipolar disorder.

11. **Developing new treatments for depression**. Depression and anxiety disorders are common mental disorders. There are currently many drugs in use for depression; however, the majority of these drugs take from weeks to months to reach efficacy. The reasons for the prolonged time course of antidepressant action are unknown. Recently, however, rapid-acting antidepressant drugs have been identified. For example, the effects of ketamine in depressed patients suggest that one promising mechanism might be through the mammalian target of rapamycin (mTOR), which results in new protein synthesis and the formation of new dendritic spines. This research raises the possibility of new classes of drug targets for mood disorders. Growth factors are involved in cell proliferation and differentiation, but many also regulate the formation and plasticity of neuronal networks. For example, expression of BDNF is induced rapidly in the hippocampus and the amygdala following both learning and acute stress. Scientists have hypothesized that a decrease in growth factors is directly involved in depression and other affective disorders, and may be a contributing factor in the pathogenesis of severe depression. It should be noted that enriched living conditions, exercise, and training in learning paradigms all elevate growth factors and cognitive performance. For example, transient elevation of BDNF levels facilitate plasticity and also enhance conditioning in the amygdala and memory consolidation in the hippocampus. Because exercise and antidepressants are known to dramatically increase the levels of growth factors, new treatments will come about that also involve manipulating growth factors to ameliorate depression and anxiety.

12. **Treating addictive disorders**. Addictive disorders are diseases of the brain that proceed through a more or less stereotypic set of milestones that have an impact on key molecules and brain circuits, and that eventually compromise the higher order processes that orchestrate emotions, cognition, and behavior. Despite clear trajectory differences

stemming from variations in an individual's constitution and a drug's effects, both animal and human studies have shown that addiction involves expanding cycles of adaptive dysregulation in the brain. The better understanding that we have today of addiction circuitry is ushering in a host of smart strategies that may be combined, personalized, and targeted to be more effective. Although the term "addiction" has traditionally been equated with a person's impaired control over substance-use behaviors, there has been a recent shift toward considering other non-substance-related circuitries. The shift may be justified insofar as many addictive disorders do display the central feature of loss of control over a specific behavior (e.g., gambling, eating, sex), resulting in predictable, adverse, sometimes catastrophic consequences. Furthermore, there is growing neurophysiologic evidence to suggest substantial functional and neurocircuitry overlap, at least in pathological gambling, eating disorders, and substance use disorders (SUDs). Therefore, future comparative addiction research is poised to significantly enrich the detailed picture we already have of substance use disorders. Conversely, today's researchers have a great opportunity to harness the vast knowledge we currently possess about SUDs to better understand the etiology and trajectories of less-studied addictive disorders. Indeed, there are many lessons to be learned from decades of fertile research into the contributors to, prevention of, and treatment of these conditions. In addition, these disorders often involve cycles of abstinence and relapse, and there is a great need for interventions that modify the risk of relapse.

13. **Improving treatment of schizophrenia**. Schizophrenia is a highly impairing chronic condition, associated with psychotic symptoms (such as delusions and hallucinations), cognitive symptoms (related to impaired working memory), and negative symptoms (e.g., amotivation, impoverished speech). Exploitation of highly penetrant genetic risk factors, such as the gene DISC-1 promises to identify developmental pathways that could yield disease-altering drug targets. In parallel, the combination of cognitive neuroscience and neuroimaging has made it possible to being to develop treatments for the highly-disabling cognitive symptoms of schizophrenia.

14. **Preventing and treating cerebrovascular disease.** Cerebrovascular disease accounts for a large percentage of the costs of death and

disability in the US population. As the baby boomer generation ages, this burden will increase dramatically. Although rupture or blockage of a blood vessel to or in the brain is the ultimate cause of stroke, both environmental and genetic factors influence susceptibility. Detailed phenotyping has isolated several genetic loci that play a role in subsets of stroke patients. Each new gene has the potential to be a therapeutic target. Prevention is, of course, the best approach, and as with heart disease, significant changes are possible through lifestyle changes and medical management. Recovery and rehabilitation post-stroke are improving rapidly, and further advances are expected based on research findings on neural regeneration, stem cell technology, and connectomics. In the future, genetics will provide clues to people's risk factors for stroke; internists will provide a prevention plan; new strokes will be evaluated on site by telemedicine; medication will be administered; and, if intervention is necessary, the patient will be transferred to centers that can provide intervention. Completed strokes will be treated with growth factors, stem cells, focused rehabilitation, and attention to preventing recurrences.

15. **Achieving personalized medicine**. The goal of matching patients with the safest and most effective treatments for them is highly laudable. In lung cancer, for example, specific mutations within some cancer cells can now predict response to particular drugs in a minority of cases. For brain disorders, the idea of personalized medicine is in its infancy. Progress will depend on substantial advances in genetics, including the genetics of treatment response, the deep phenotyping of many individuals, advances in bioinformatics, and a culture of data sharing.

16. **Understanding shared mechanisms of neurodegeneration.** Many neurodegenerative disorders are characterized by misfolding of proteins and this event marks a critical aspect of pathogenesis. The proteins found in the aggregates that characterize many of these disorders are, in many cases, products of genes that have been shown to be mutated in familial forms of the disease. Whatever the mechanism, the possibility exists that methods to prevent misfolding and/or to enhance refolding can be envisioned to prevent or reverse pathogenic mechanisms.

17. **Advancing anesthesia.** General anesthesia is a drug-induced reversible condition characterized by unconsciousness, lack of pain, inability to

remember, and lack of movement with maintenance of physiological stability. It is crucial for performing most surgical and many medical procedures. In the United States alone, 21 million people have general anesthesia yearly for surgery. The way in which anesthetic drugs induce this state of reversible coma—not sleep—is considered a major mystery of modern medicine, despite their use for more than 165 years. Current anesthesiology research is focused on anesthetic drug pharmacology and on identifying molecular targets of these agents, and it has been critical for establishing principled approaches to anesthetic drug dosing. In the next ten years, the mystery of how anesthesia works can be solved by taking several key steps. First, anesthesiology researchers must use their current understanding of molecular pharmacology in studies of general anesthesia that apply the latest functional imaging and neurophysiology techniques. Second, anesthesiology research must draw from and contribute to research in other areas of clinical neuroscience. No clinical neuroscience discipline actively manipulates the state of the brain and central nervous system more than anesthesiology. This enormous clinical experience has not been translated into new insights for anesthesiology or for other areas of clinical neuroscience. Fundamental links can and should be made formally between anesthesiology and psychiatry (the anesthetic ketamine is now being used to treat depression, and as a model for schizophrenia), neurology (opioids and antipsychotic drugs simulate Parkinsonian and locked-in states), coma recovery and intensive care (medically- and hypothermia-induced comas are actually states of general anesthesia, and monitoring the brain under general anesthesia is equivalent to monitoring the brain of a patient in intensive care), and sleep research. Third, anesthesiology must revise its residency and continuing medical education programs to include a stronger emphasis on neuroscience. For example, the electroencephalogram shows characteristic pattern changes according to the state of general anesthesia, but anesthesiologists are not trained to interpret these patterns. A broader use of neuroscience in anesthesiology will significantly improve patient care by facilitating the development of more site-specific anesthetic drugs with fewer side effects, and more neurophysiologically sound approaches to monitoring the states of the brain under general anesthesia. Finally, anesthesiologists must educate their medical colleagues and the public about what general anesthesia is. By assuming its role as a full partner in clinical

neuroscience, the field of anesthesiology will improve its practice in other clinical neuroscience fields as well as enhancing our fundamental understanding of the brain's arousal, pain, and cognitive systems.

TOOLS AND TECHNOLOGIES FOR CLINICAL NEUROSCIENCE

1. **Remote monitoring technologies.** These can assess physiological stress and affect as a means to prevent episodes of illness. Technological advances now make it possible to envision a time very soon in which a patient's vital signs, EEG, EKG, and movements can be recorded 24/7 and sent wirelessly to a remote location for review by a physician. This 'neurosensory suit' could record up to 1,000 channels of EEG in real time, as well as monitoring vital signs and even subtle aspects of movement. With further development, the suit might be deployed to allow neurologists a much more complete assessment of patients with a variety of disorders, in the process collecting many thousands of times as much data as is currently the case. Advances in diagnosis, disease profiling, and management will follow**.**

2. **Imaging of the brain in real time**. There will be an increasing ability to define the operation of brain circuits in real time. This will make possible ever-more-revealing insights into the operations of circuits as well as their failure to operate in disease states.

SPECIFIC OPPORTUNITIES AND TOOL BUILDING GOALS CAN BE FOUND AT

www.1mind4research.org

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