

# Targeted Research: Brain Disorders as an Example

## A Vital Direction for Health and Health Care

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### Introduction

Much discussion surrounds the question of the most appropriate strategies for bringing the power of science to bear on the nation's pressing problems. Some problems, such as an emerging infectious disease, are urgent and must be addressed immediately. Others, such as the increasing global burden of dementia and other neurodegenerative diseases as populations grow older, become apparent with time but can be just as pressing in their implications. Advances in science and technology are often critical for progress, and circumstances can make it imperative for major science-based initiatives to deal with problems. We argue here that now is the right time for a substantial science-based assault on disorders of the brain. Our thesis is based on the conjunction of a growing worldwide societal burden of brain disorders with scientific opportunity driven by the maturing of neuroscience

and related disciplines, by the recent and continuing emergence of relevant tools and technologies, and by the quality and number of personnel in the field.

### Policy Strategies

There is no simple recipe for the planning and conduct of science-based initiatives that would ensure advances in both scientific progress and their application to societal problems. Much, however, has been learned from prior science initiatives. The temptation is always great, particularly when funding is constrained, to focus research funding in explicit or targeted ways, specifying in detail the exact problems to be solved and even the research approach to be taken. But the history of American science shows that stipulation of details can be counterproductive. What has generally been proved most effective is a combination of approaches to the support of research and development

that involves diverse strategies. Moreover, it should be emphasized that increased funding, although almost always a necessary condition for progress, will not by itself yield solutions to critical problems. The science must be tractable—even if difficult—and there must be an appropriate workforce in the field in question or workers willing to enter from related fields. Both those conditions prevailed in the response to HIV/AIDS that began in the 1990s.

In addition to substantial increments in funding, policy and regulatory initiatives may be required to advance relevant science and to apply it effectively to the pressing problems that motivated the investment. Policy initiatives involving regulatory and possibly legislative bodies, the academic and industrial sectors, and journal publishers can markedly increase the likelihood of successful research and societal outcomes. Examples include the sharing of data (in conjunction with appropriate ways of protecting the privacy of individuals), the sharing of methods and key reagents by scientists, increased incentives for scientific rigor (as opposed to premature publication), and decreased barriers to partnerships between academic and industrial researchers that address the issue of conflicts of interest.

If increased funding and appropriate policy interventions set the stage for acceleration of progress, decisions must be made about strategies for funding projects. Different federal agencies use different approaches. One funding approach is largely undirected or unconstrained: almost every technically sound project proposal is considered, and funding decisions are made solely on the basis of scientific merit as determined by peer review. That “unsolicited” approach has been particularly effective for such agencies as the National Science Foundation (NSF), whose mission is the broad support of virtually all fields of basic or fundamental science. NSF-funded research has produced many important discoveries, often with benefits to society that were initially wholly unexpected. An excellent example of such an unexpected benefit is the diverse science underpinning intelligent learning systems, which has led to an enormous number of applications, such as speech-recognition technology and powerful data-analysis tools that are used throughout academe, many industries, and government. A complementary funding approach is to target specific questions or problems that need to be answered or specific

technologies that are needed by end users and then to solicit responsive proposals. In its extreme version, the “directed” approach might specify timelines and much detail about the desired products. Such agencies as the Defense Advanced Research Projects Agency (DARPA) typically use this approach, and their efforts have resulted in many important advances, often with clear utility. The National Institutes of Health (NIH) has successfully used a combination of approaches whereby some biomedical research projects are supported as a result of unsolicited proposals and others are supported as a result of targeted requests for applications. Such a hybrid approach is recommended for the initiative proposed here.

A major goal of special initiatives is to draw researchers to work on particularly difficult or urgent questions and challenges. Such initiatives usually direct a substantial stream of targeted funding to a problem. They typically use a variety of approaches, which may ultimately be specified by a funding agency through such mechanisms as requests for applications. Most successful efforts are initially grounded in consultations and workshops among diverse members of the investigator community. One of the largest such efforts was directed against HIV/AIDS. For over 20 years, 10% of the NIH budget was set aside to support HIV/AIDS research; some of the research projects were specified by the agency, and others were “bottom-up” projects proposed by members of the scientific community. Because of the size and complexity of the effort, it was overseen by the Office of AIDS Research, which coordinated work among NIH Institutes and ensured that grants made under the rubric of HIV/AIDS research were germane to the problems at hand. That approach contributed substantially to the transformation of HIV infection from a death sentence to a manageable chronic illness and to success in prevention of transmission. NIH recently determined that the challenges that remain with respect to HIV/AIDS—such as understanding viral reservoirs and developing a vaccine—no longer require the longstanding set-aside of funds.

Dedicated funding targeted to a particularly promising basic-science subject resulted in the great feat of sequencing the human genome. It is important to recognize the enormous value that that effort generated: not only was an initial human-genome reference sequence published, but the development of technologies and computational tools that have revolutionized

biomedical science was directly supported and encouraged. The rapid decrease in costs of sequencing DNA and the increase in the ability to analyze and understand the resulting data have led to a truly remarkable acceleration in identification of genetic contributors to many diseases, which in turn is beginning to influence diagnostics and discovery of therapies throughout medicine. The return on investment has been extraordinary, not only scientifically but economically: nearly \$1 trillion in economic growth for a 178-fold return on investment (Batelle Technology Partnership Practice, 2013).

Another dramatic example is provided by approaches to cancer (an umbrella term for a diverse family of illnesses that have different etiologies, molecular mechanisms, treatment responses, and outcomes). President Nixon declared a War on Cancer in 1971, and cancer research has since periodically received substantial infusions of funds. The increases in funding have undoubtedly contributed to the transformation of some cancers from untreatable, rapidly lethal diseases into chronic conditions that can be managed over increasing periods of survival or in some cases cured. Cancer biologists and clinicians faced scientific challenges, but they also benefited from scientific opportunity—direct access to living tumor tissue excised in biopsies or in surgical treatments and in more recent years the ability to sequence the genomes of large numbers of cancer cells from diverse tumor types. In his January 2016 State of the Union address, President Obama announced a new initiative in cancer, a Cancer Moonshot that has such goals as accelerating progress by focusing on preventive vaccines, early detection, immunotherapy, pediatric cancer, and data sharing (Lowy and Collins, 2016).

As we have emphasized, a funding initiative does not by itself make a particular set of scientific problems immediately tractable, nor does it ensure effective handoffs from academic or government scientists to industry or the development of safe and effective preventive interventions or treatments. However, in addition to supporting relevant research directly, funding initiatives can attract established researchers to a field, influence the popularity of a field among trainees, and gain the attention of academic and industrial developers of technology. Those effects have certainly resulted from the initiatives with HIV/AIDS and cancer research. One of the great benefits of the genome project was

its focus on supporting technology development even as it increased the size of the market for ever more sophisticated DNA-sequencing machines. New federal investment in a field can also lead to reexamination and reform of regulation, such as the passage of the Genetic Information Nondiscrimination Act of 2008, which prohibits the use of genetic information in employment and health insurance.

### Brain Disorders Are Ripe for Special Attention

The key factors that now motivate a proposal for an initiative on brain disorders are the rapidly advancing tools and knowledge to facilitate understanding of disease mechanisms, a strong and growing scientific workforce in neuroscience, and a substantial mismatch between research investment and unmet medical need, global disease burden, and rising costs to societies (Bloom et al., 2011; Murray et al., 2013). The need for research investment is highlighted by the growing global prevalence and costs of neurodegenerative disorders (Hebert et al., 2013; Hurd et al., 2013) and a large disinvestment by industry in brain disorders since 2010 (Choi et al., 2014) with the possible exception of Alzheimer disease clinical trials. The withdrawal of industry is in large part a consequence of gaps in molecular-target identification and validation and in biomarkers, in contrast with such diseases as cancer that have been the beneficiaries of many initiatives that have brought resources to bear. The consequence for the preponderance of brain diseases—such as autism, epilepsy, depression, schizophrenia, and stroke—is that the translation of emerging neuroscience is impeded. If the current Alzheimer disease trials fail, even this industry commitment to therapy development will disappear, as did the commitment to stroke therapies after trials failed.

The initiative proposed here would capitalize on new technologies and rapidly emerging scientific discoveries to create a new effort focused on identification and validation of molecular targets and identification of biomarkers. In the language of industry, such efforts would “derisk” brain-disorders research and thus decrease the barriers to reentry for companies. It is clear that new technologies and scientific advances can accelerate therapy development. For example, the use of magnetic resonance imaging to screen potential neuromodulatory treatments for multiple sclerosis has

resulted in the successful development of a number of therapeutic agents that slow disease progression. The discovery that dopamine was depleted in Parkinson disease led to the development of dopamine replacement therapy, and elucidation of the brain circuitry that is perturbed in Parkinson disease led to treatment with deep brain stimulation that transforms the lives of patients in the middle stage of the disease.

Brain disorders as diverse as autism and Alzheimer disease are increasingly addressable by biomedical science. That point is critical. The complexity of the human brain and its inaccessibility to direct examination during life have rendered the study of brain disorders extremely challenging, but the last decade has seen the development of diverse technologies that permit a concerted attack on these illnesses. The recognition of the great and growing burden of brain disorders on society and the extraordinary recent progress in brain research and in the development of technologies for such research make the disorders particularly ripe for special attention. An initiative could lead to important improvements in the lives of patients and their caregivers while accruing substantial economic benefits by decreasing levels of disability.

Over 100 million Americans suffer from brain disorders, including mental illnesses, neurologic disorders, and addiction. According to NIH, one-fourth of Americans suffer from a diagnosable mental disorder at some point in their lives. Over 50 million Americans suffer from neurologic disorders, including over 5 million from Alzheimer's disease alone. The World Health Organization's *Global Burden of Disease* study (Murray et al., 2013) showed that brain disorders are the leading cause of disability in the United States; they are also the largest cause of financial loss due to noncommunicable disease. The World Economic Forum and Harvard School of Public Health estimated the global financial cost of mental illnesses in 2010 at US\$2.5 trillion per year and the expected cost by 2030 at US\$6 trillion. A science-focused initiative would contribute to a great reduction in both personal and financial costs.

It is important to recognize how difficult it has been to carry out the science needed to deal with those disorders effectively and what is involved. Understanding the structure and function of the human brain remains extremely challenging. The human brain is the most complex organ; it has more than 80 billion neurons, and there are 5,000 or more types of neurons and glial

cells. Each neuron has about 1,000 connections (synapses) with other neurons, but the range is vast. The roughly 100 trillion synapses in the human brain give rise to the neural circuits that underlie the computations that produce sensation, cognitive function, emotion, motivation, and the control of behavior. Long-lasting changes in synaptic connections and circuits are the basis of learning and memory. Abnormalities in the structure and functioning of brain cells, synapses, and circuits are responsible for the diverse symptoms and impairments that result from brain disorders.

Much as Galileo could not have advanced understanding of the solar system without a telescope, new tools developed in the last decade have revolutionized the life sciences in general and neuroscience in particular. They include genomic technologies and computational tools, which resulted in large part from the Human Genome Project; stem-cell technologies; genome engineering tools, such as CRISPR-Cas9; and, of particular importance to neuroscience, rapidly advancing technologies to study and even control activity in the cells and circuits of living brains and to provide useful maps of connectivity, such as those emerging from the Human Connectome Project and from the Allen Institute for Brain Science. The development of transformative tools and technologies, too often neglected, is critical for advances in our understanding of how the brain works and the development of better diagnoses and effective treatments for brain disorders. For example, advanced tools to study the expression of genes in single cells were described last year and are already being applied to the analysis of diverse cell types in the brain, but the actual mapping of particular protein complexes—the intended targets of drugs—to particular neural cell types awaits further development.

Federal funding has rarely been used to support the creation and dissemination of research tools and technologies, although there are notable exceptions, as in the Human Genome Project. Recognizing the great opportunities provided by recent advances in brain research coupled with the critical need for new technologies, a group of federal agencies and private foundations have joined forces and committed funds to the BRAIN (Brain Research through Advances in Innovative Neurotechnologies) Initiative. That initiative, a 12-year public-private partnership, was begun in 2013 and aims to provide the new tools and technologies needed to accelerate understanding of normal and

abnormal brain structure and function. The current federal partners include NSF, NIH, DARPA, the Intelligence Applied Research Projects Agency, and the Food and Drug Administration. The private foundations in the partnership include the Howard Hughes Medical Institute, the Simons Foundation, the Allen Institute for Brain Science, and the Kavli Foundation. The collaborative focus of so many participants and funding organizations on developing new technologies and using them to elucidate brain circuitry is unprecedented. The BRAIN Initiative, with its focus on technology development and the normal brain, is essential in elucidating how the brain processes information and initiates behavior, and it should continue to be supported. However, it is only the beginning for understanding brain disorders. To address those, it is essential that newly developed technologies be applied to further understanding of human brain structure and function in health and disease. Moreover, the integration of advances arising from the genetic dissection of brain disorders with the kinds of tools and technologies emerging from the BRAIN Initiative is likely to be critical if gene lists are ultimately to be translated in a manner that improves human health.

### Elements of an Initiative on Brain Disorders

This proposal is based on the pressing need to improve the prevention of and treatment for early-onset neuropsychiatric and neurodegenerative disorders. The highly damaging effects of these conditions on individuals, families, and society have been well documented by studies of disease burden, direct costs of health care, and economic loss.

Perhaps the greatest impediment to progress in preventing and treating brain disorders has been the incomplete knowledge of normal brain function coupled with slow progress in understanding their detailed pathophysiology, including molecular mechanisms of disease. Much can be learned from how progress has been made in cancer biology, even though diseases of the nervous system bring even greater challenges. Identification of molecular mechanisms and therapeutic targets in cancer has been rapidly advanced by sequencing the genomes of many surgically obtained cancer cells under a variety of large-scale efforts supported by the National Cancer Institute, beginning with the *Cancer Genome Atlas* in 2005. That approach

is feasible because of the centrality of highly penetrant acquired mutations in the origin of most cancers notwithstanding the complexities of tumor heterogeneity and of distinguishing the mutations in cancer cells that drive pathogenesis from the welter of passenger mutations.

The identification of molecular mechanisms of pathogenesis in brain disorders has been more difficult. Despite well-known examples of rare monogenic disorders of the nervous system, such as Huntington's disease and rare familial forms of amyotrophic lateral sclerosis, genetic risk factors for the vast majority of psychiatric, neurologic, and addictive disorders are carried by large numbers of modestly penetrant genetic variants. Thanks to the revolution begun by the Human Genome Project, what had seemed an insuperable problem has begun to yield rapidly to modern genomic technologies being brought to bear on specific disorders by large global consortia. Perhaps unrecognized in the broader scientific community, those efforts have achieved remarkable success related to many conditions, including autism, epilepsy, schizophrenia, bipolar disorder, and common, late-onset forms of Alzheimer's disease. Those growing success stories also reveal that the genetic analysis of brain disorders is scalable, and with appropriate organization and good policies (such as requirements for data-sharing within the bounds of protecting subject privacy) additional funding would efficiently advance the pace of discovery and thus accelerate investigations into disease mechanisms (Sekar et al., 2016), the nomination of molecular targets for therapies, and the discovery of candidate biomarkers (Jack and Holtzman, 2013).

It has often been objected that neuroscience has been unable to exploit even Mendelian genetic discoveries for therapies, notably for mutations that alter protein function, such as the gene in which triplet repeats cause Huntington's disease. In fact, the challenge of therapy for Huntington's disease is not dissimilar to that facing therapy for monogenic hematologic disorders, such as sickle-cell disease, in which the causative amino acid variation has been known since the 1950s: both in Huntington's disease and in monogenic hematologic disorders early attempts at gene therapy are proceeding in parallel. The deeper problem that calls for a scientific initiative is how to study pathogenesis of common polygenic brain disorders—how to use rapidly emerging genetic results to inform useful biologic

experimentation and ultimately therapy. The problem of polygenicity is, at one level, no different from that in studying immunologic disorders or metabolism—although it is of note with respect to metabolism that essentially all the genetic regulation of body-mass index maps to the brain, not liver, pancreas, gut, or adipocytes.

A focus on brain disorders is warranted by its contribution of lifetime disease burden and by the promising technologic advances created by the BRAIN Initiative and the development of tools that are advancing all biology, such as stem-cell technologies, production of organoids, and genome engineering technologies.

The initiative proposed here is meant to advance and make more widely available platform technologies and data sharing through increased funding and policy initiatives and to enhance collaboration between academe and industry to advance the translation of basic findings as they mature. An example of a successful public-private consortium that could be used as a model for new collaborations is the Alzheimer's disease neuroimaging initiative (ADNI) which played a key role in the identification and implementation of biomarkers for Alzheimer's disease in clinical trials.

Specific components of the initiative proposed here include the following set of actions:

- Encourage and support the formation of new consortia to advance genetic and phenotypic analyses of brain disorders in diverse populations and to collect biospecimens that, among other things, will permit the production of induced pluripotent cell lines and organoids.
- Combine those efforts with policy initiatives to encourage sharing of data, cell lines, and other materials in a manner that is consistent with the protection of privacy. Create infrastructure to support secure data storage, data sharing, and the banking of biologic materials.
- Increase funding for the dissemination of cell lines, animal models, technologies, and software packages. Policy initiatives involving funders and journals are needed to ensure the availability of detailed scientific methods to enhance replicability of results.
- Support completion of the initial goals of the BRAIN Initiative to ensure that the necessary tools and technologies are available to study normal and pathologic brain function, including fundamental understanding of neural-cell types and circuits.
- In parallel, support expansion of the BRAIN Initiative to provide tools and to produce and study both in vitro (cellular, organoid, and explant) models and in vivo models of brain disorders on the basis of insights coming from genetics. Accelerate technology development to study the human brain.
- Support advances in human experimental biology (for example, using new physiologic and imaging technologies derived from the BRAIN Initiative) to investigate candidate biomarkers coming from genetic analyses and, when possible, disease pathogenesis.
- Encourage and support empirical investigations and ethical analyses to investigate emerging concepts of privacy among cultures and age groups and the risk tolerance of patients and families for participating in genetic and phenotyping studies that involve longitudinal participation and data sharing (with attendant risks to the privacy of their personal data).
- Support training of clinicians in the interpretation of genetic data and their clinical utility while increasing the number of genetic counselors being trained.
- Facilitate the development of and identify funds for public-private initiatives (using such models as ADNI and the Accelerating Medicines Partnership) on topics that include biomarker discovery and target validation. Development of appropriate policies for partnerships will require involving both regulatory and funding agencies from the outset.
- Explore avenues to facilitate the adaptation of the most promising biomarker candidates for early diagnosis of neuropsychiatric and neurodegenerative disorders to allow interventions at the earliest possible time, when they are most likely to be effective.

## Summary Recommendations for Vital Directions

1. Create new models for large-scale research consortia and public—private partnerships.
2. Develop new tools and technologies for research.
3. Establish policies and infrastructure for banking of biospecimens, storage of data and software, and their sharing, and develop effective approaches to dissemination of knowledge, tools, and reagents.

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