



NATIONAL INSTITUTE  
OF MENTAL HEALTH

Strategic Plan  
for Research



National Institute  
of Mental Health



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# Table of Contents

<b>Director’s Message</b> .....	<b>4</b>
<b>Introduction</b> .....	<b>6</b>
Adapting to a Changing Ecosystem .....	8
Cross-Cutting Research Themes .....	12
Highlight: What Is RDoC? .....	16
Highlight: What Is a Target? .....	17
Accomplishing the Mission .....	18
<b>Strategic Objective 1: Define the Mechanisms of Complex Behaviors</b> .....	<b>21</b>
Strategy 1.1: Describe the molecules, cells, and neural circuits associated with complex behaviors .....	23
Strategy 1.2: Identify the genomic and non-genomic factors associated with mental illnesses .....	24
Strategy 1.3: Map the connectomes for mental illnesses .....	25
Highlight: Disease-in-a-Dish .....	27
Highlight: Skyline Drivers .....	28
Highlight: Slicing Optional .....	29
<b>Strategic Objective 2: Chart Mental Illness Trajectories to Determine When, Where, and How to Intervene</b> .....	<b>31</b>
Strategy 2.1: Characterize the developmental trajectories of brain maturation and dimensions of behavior to understand the roots of mental illnesses across diverse populations .....	32
Strategy 2.2: Identify clinically useful biomarkers and behavioral indicators that predict change across the trajectory of illness .....	33
Highlight: Beautiful Convolutions .....	34
Highlight: GPS for the Brain? BrainSpan Atlas Offers Clues to Mental Illnesses .....	35

**Strategic Objective 3: Strive for Prevention and Cures..... 37**

- Strategy 3.1: Develop new treatments based on discoveries in genomics, neuroscience, and behavioral science..... 38
- Strategy 3.2: Develop ways to tailor existing and new interventions to optimize outcomes ..... 39
- Strategy 3.3: Test interventions for effectiveness in community practice settings ..... 40
  - Highlight: Toward Signposts for Precision Medicine..... 41
  - Highlight: Ketamine: A New (and Faster) Path to Treating Depression..... 42

**Strategic Objective 4: Strengthen the Public Health Impact of NIMH-Supported Research..... 45**

- Strategy 4.1: Improve the efficiency and effectiveness of existing mental health services through research ..... 46
- Strategy 4.2: Establish research-practice partnerships to improve dissemination, implementation, and continuous improvement of evidence-based mental health services ..... 47
- Strategy 4.3: Develop innovative service delivery models to improve dramatically the outcomes of mental health services received in diverse communities and populations..... 48
- Strategy 4.4: Develop new capacity for research that evaluates the public health impact of mental health services innovations ..... 49
  - Highlight: Learning Mental Health System—Narrowing the Gap from Science to Service..... 50
  - Highlight: A Therapist in One’s Pocket: mHealth to Improve Access to Mental Health Care..... 51

**Appendix: Development and Comment Process for the NIMH Strategic Plan for Research..... 52**

**References..... 53**



## Director's Message

The National Institute of Mental Health (NIMH) has just entered its 66th year as the Nation's leader in research on mental disorders, supporting research to transform the understanding and treatment of mental illnesses, paving the way for prevention, recovery, and cure. Over the past 6 years, we have seen progress in many areas, from fundamental neuroscience to research on service delivery. We have seen breakthroughs in genetics, the launch of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, and the success of the Human Connectome Project. We have completed a study of risk and resilience in more than 100,000 soldiers and developed the Early Psychosis Prediction and Prevention (EP3) program to prevent

the onset or reduce the duration of untreated psychosis. When we compare these accomplishments against our goals in the 2008 Strategic Plan, we see what forward planning can accomplish. While there has been progress, we believe much more is possible. This update of our Strategic Plan is a commitment to take a fresh look at our horizons so that we can refine priorities and energize our path of discovery.

We know that some scientists reject the concept of "directed science," believing that science rarely follows a plan. True, important discoveries often result from serendipity or side roads rather than a premeditated, carefully articulated strategy. On the other hand, these "eureka moments" come to those working on tough problems. A strategic plan can identify the most important problems and identify areas of traction. And for our science to affect policy or practice, a plan may be essential. In fact, the right plan can serve both scientific discovery and public health needs. With this realization in mind, and with the guidance of the National Advisory Mental Health Council and our public stakeholders, we updated the 2008 Strategic Plan. During this process, we heard three questions repeatedly:

**First: How do we balance urgent mental health needs with longer-term investments such as basic research?** The unavoidable tension between patients' urgent needs today and the promise of basic science progress on the horizon is daunting and particularly critical with limited funds. In fact, we need to focus on both near-term and long-term objectives. Near-term needs can be pursued strategically through targeted funding announcements with deliverables and timelines. Our longer-term objectives are best pursued via supporting investigator-initiated proposals based on scientific opportunities that lead to fundamental discoveries. But we avoid investing research dollars based on a predetermined formula of short-term versus long-term impact.

**Second: How do we link advances in biology (e.g., genomics, neuroscience) with the range of environmental factors (e.g., stress, social determinants) that influence mental disorders?** While the tools of genomics and neuroscience now permit rapid progress, equivalent tools and paradigms to study environmental influences are just being developed. Over this next 5-year period, we can expect this new approach to environmental factors, sometimes called the exposome, to yield more scientific traction in understanding the mechanisms by which environmental factors alter brain and behavior, from prenatal development through the process of aging.

**Third: What are the metrics of success? That is, how will NIMH know whether and when it has met its goals?** While the discovery phase of science may not lend itself to timelines and milestones, being more strategic in our planning necessitates accountability. Our success cannot be measured solely by traditional academic "outputs": the numbers of grants supported or papers published. Our success needs to be assessed by "outcomes": how well the research we support changes our understanding of brain and behavior, improves our diagnostic system, provides effective treatments, supports prevention of mental disorders, eliminates the disparities in underserved populations, and reduces premature mortality among persons with mental illnesses. We will position ourselves to collect the appropriate metrics to provide credible answers to these and other important questions.

This Plan is our commitment to accelerate the pace of scientific progress by generating research over the next 5 years that will have the greatest public health impact and continue to fuel the transformation of mental health care. We at NIMH trust that you find the prospects as exciting and important as we do.

Thomas R. Insel, M.D.  
Director, NIMH

# Introduction

The National Institute of Mental Health (NIMH) is the lead Federal agency for research on mental illnesses.<sup>1</sup> The mission of NIMH is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure.

The urgency of this mission arises from the public health burden. According to recent estimates, mental illnesses account for 21.3 percent of all years lived with disability in the United States.<sup>1</sup> An estimated 9.6 million American adults suffer from a serious mental illness (SMI) in which the ability to function in daily life is significantly impaired. Those with SMI die 10 years earlier than individuals in the general population, on average.<sup>2</sup> Furthermore, over 40,600 Americans die each year from suicide, more than twice the annual mortality from homicide or AIDS.<sup>3</sup> Beyond the morbidity and mortality, a conservative estimate places the direct and indirect financial costs associated with mental illnesses in the United States at well over \$300 billion annually.<sup>4</sup> Mental illnesses rank as the third most costly medical conditions in terms of overall health care expenditure, behind heart conditions and traumatic injury.<sup>5</sup>

This public health burden demands that we harness scientific knowledge and tools to achieve better understanding, treatment, and ultimately, prevention of these disabling conditions. We must do better. To fulfill its mission, NIMH:

- **Supports and conducts research on mental illnesses and the underlying basic science of brain and behavior.**
- **Supports the training of scientists to carry out basic and clinical mental health research.**
- **Communicates with scientists, patients, providers, and the general public about the science of mental illnesses.**

Fundamental to our mission is the proposition that mental illnesses are brain disorders expressed as complex cognitive, emotional, and social behavioral syndromes. Progress depends on advances in basic behavioral science and fundamental neuroscience, in addition to clinical science.

<sup>1</sup> This Strategic Plan for Research uses the terms “illness” and “disorder” interchangeably. These terms are used to refer equally to brain disorders expressed as complex cognitive, emotional, and social behavioral syndromes.

In 2008, NIMH published a Strategic Plan to accelerate progress in both basic and clinical science. This Plan was limited to research, with separate planning efforts for training and communication. With the remarkable growth in scientific findings during the past 6 years, and the changing landscape of mental health care, the need to update the Plan became clear. Several other strategic plans have informed our planning and include more detail on specific topics, such as the *National Research Action Plan (NRAP)*<sup>ii</sup> addressing post-traumatic stress; the *Interagency Autism Coordinating Committee Strategic Plan for Autism Spectrum Disorder Research*;<sup>iii</sup> *A Prioritized Research Agenda for Suicide Prevention: An Action Plan to Save Lives*,<sup>iv</sup> a collaboration with the the National Action Alliance for Suicide Prevention; and the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Working Group Report.<sup>v</sup> NIMH also has a substantial investment in supporting

AIDS research; it is important to note that this investment is guided by a National Institutes of Health (NIH)-wide Strategic Plan<sup>vi</sup> coordinated through the NIH Office of AIDS Research; as such, research on the mental health aspects of AIDS is not addressed in the current Plan.

In this new Strategic Plan for Research, with the goals of helping individuals living with mental illnesses and promoting both prevention and cure, NIMH has revised the original four, high-level Strategic Objectives (SOs) as follows:

- 1. Define the mechanisms of complex behaviors.**
- 2. Chart mental illness trajectories to determine when, where, and how to intervene.**
- 3. Strive for prevention and cures.**
- 4. Strengthen the public health impact of NIMH-supported research.**

.....

<sup>ii</sup> For the NRAP, see: [https://www.whitehouse.gov/sites/default/files/uploads/nrap\\_for\\_eo\\_on\\_mental\\_health\\_august\\_2013.pdf](https://www.whitehouse.gov/sites/default/files/uploads/nrap_for_eo_on_mental_health_august_2013.pdf) [PDF - 2.2 MB].

<sup>iii</sup> For the *Interagency Autism Coordinating Committee Strategic Plan for Autism Spectrum Disorder Research*, see: [http://iacc.hhs.gov/strategic-plan/2013/IACC\\_2013\\_Strategic\\_Plan.pdf](http://iacc.hhs.gov/strategic-plan/2013/IACC_2013_Strategic_Plan.pdf) [PDF - 7.85 MB].

<sup>iv</sup> For *A Prioritized Research Agenda for Suicide Prevention: An Action Plan to Save Lives*, see: <http://actionallianceforsuicideprevention.org/sites/actionallianceforsuicideprevention.org/files/Agenda.pdf> [PDF - 3.7 MB].

<sup>v</sup> For the BRAIN Initiative Working Group report *Brain 2025: A Scientific Vision*, see: <http://www.braininitiative.nih.gov/2025/BRAIN2025.pdf> [PDF - 1.95 MB].

<sup>vi</sup> For the *Trans-NIH Plan for HIV-Related Research*, see: <http://www.oar.nih.gov/strategicplan/fy2015/index.asp>.



These four Strategic Objectives form a broad roadmap for the Institute’s research priorities over the next 5 years, beginning with the fundamental science of the brain and behavior, and ending with public health impact. Our overall funding strategy is to support a broad spectrum of investigator-initiated research in fundamental science, with increasing use of Institute-solicited initiatives for applied research where public health impact is a short-term measure of success. Full implementation of these Strategies, will, we hope, transform the diagnosis, treatment, and prevention of these devastating illnesses.

## ADAPTING TO A CHANGING ECOSYSTEM

The purpose of the NIMH Strategic Plan for Research is not only to convey the next steps on the path to realizing the Institute’s vision, but also to provide the context and rationale for why we have chosen this particular path. Good stewardship of public funds necessitates constant surveillance of the ecosystem within which the Institute functions and adaptation when the situation demands it. The field of mental health has witnessed substantial change and progress since 2008. This section highlights the major ways in which the ecosystem has changed and how the Institute is adapting.



### **The Increasing Public Health Burden**

Mental illnesses remain an urgent public health issue. Media coverage of mass shootings, celebrity suicides, and the high rates of mental illness in prisons and among the homeless have increased the Nation’s attention on the need for better mental health care. With the increasing suicide rate in the military, as well as hundreds of thousands of service members returning with post-traumatic stress disorder (PTSD), traumatic brain injury, and depression, a White House Executive Order and members of Congress have called for an intensive response to the “invisible wounds” of war. The increasing prevalence of autism, which rose from 1 in 150 in 2008 to 1 in 68 in

2014, demands both research and expanded care. Together, these changes not only contribute to the increasing public health challenge, they also reveal the need for a deeper understanding of mental illnesses and their treatments.

## The BRAIN Initiative

The BRAIN Initiative,<sup>vii</sup> announced by President Obama in April 2013 as the “next great American project,” is supporting the creation of new tools for decoding the language of the brain. This initiative, which NIMH co-leads with the National Institute of Neurological Disorders and Stroke, supports teams of engineers, nanoscientists, computational scientists, and neuroscientists to find new, efficient ways to monitor and manipulate brain circuits. The development of tools and technologies that will deepen our understanding of the brain’s structure and function will also give us new approaches to map aberrant brain activity

associated with mental illnesses. We have already made considerable progress on this path, progress that surpasses our predictions from 6 years ago. For instance, the Human Connectome Project has given us unprecedented multimodal maps of the healthy human brain. With this technology, in the near future we expect maps of neurodevelopment in health and illness (see S01 and S02). The deeper understanding of the brain’s structure and function made possible by these new tools and techniques will lay the groundwork for better therapeutic and preventive interventions.



*President Barack Obama is introduced by Dr. Francis Collins, Director, National Institutes of Health, at the BRAIN Initiative event in the East Room of the White House, April 2, 2013. (Official White House Photo by Chuck Kennedy)*

## The Changing Mental Health Care Landscape

The implementation of the Patient Protection and Affordable Care Act of 2010 (ACA) and the Mental Health Parity and Addiction Equity Act (MHPAEA) forecasts vast changes in mental health care. The MHPAEA requires insurance groups that offer coverage for mental health care to provide the same level of benefits that they offer for general medical treatment; the ACA defines mental health care as an “essential benefit” and extends the public reach of the requirements of the MHPAEA. However, the implementation of these laws may only apply to treatments that can meet evidence-based standards. While many evidence-based treatments exist, we lack valid metrics for measuring the quality and efficacy of care. For clinicians and other decision makers, electronic health records, smart sensors, and novel forms of care

<sup>vii</sup> “Brain Research through Advancing Innovative Neurotechnologies”; for more information, see: <http://www.braininitiative.nih.gov/index.htm>.

delivery will provide opportunities to learn from individuals with mental illnesses, and to continually apply that knowledge to improve mental health care.

The priorities outlined in the later Objectives of the Strategic Plan for Research (SO3 and SO4) will inform how we address the demands that new policies such as the ACA and the MHPAEA bring. How will the increased demand for mental health care be met? How can we ensure that evidence-based practices are implemented across diverse settings for increasingly diverse populations? What are the best methods for transferring the latest knowledge and new interventions to the workforce? The answers to these questions will need to be addressed by NIMH in partnership with the Substance Abuse and Mental Health Services Administration (SAMHSA), the U.S. Department of Veterans Affairs (VA), and others.



### **Technology**

The rapidly evolving health technology sector has the potential to radically transform the way all people (i.e., patients, providers, researchers, payers) interact within the mental health care system. Mobile technologies are changing the world of mental health care in ways that could scarcely have been imagined before the social media revolution. This is evident in the use of mobile devices as sensors to detect subtle changes in activity, and by extension, emotional state; as online extenders of individual psychotherapy;<sup>viii</sup> or as tools to move evidence-based interventions into remote communities. New methods for investigating activity within brain circuits, such as functional magnetic resonance imaging (fMRI) neurofeedback, are already being tried as treatments. And

noninvasive approaches to strengthening circuits, like cognitive training exercises—potentially offered through entertainment software and video game platforms—may open doors for researchers to build resilience and prevent mental illnesses from occurring, rather than simply reduce symptoms. The promise is enticing, but there are still many unanswered questions about effectiveness, concerns about privacy, and challenges for regulation of these nascent technologies.

### **Comparative Effectiveness**

In addition to developing new treatments, NIMH has pioneered the use of practical trials, comparing existing interventions to determine effectiveness in real-world settings. This information is critical for people with mental illness, providers, and

<sup>viii</sup> Psychotherapy is a general term for treating mental health problems by talking with a psychiatrist, psychologist, or other mental health provider.

policy makers. Such comparative effectiveness research (CER) can inform health care decisions by providing evidence of the effectiveness and/or possible harms of different treatment options. Fortunately, NIMH is no longer the only source of support for this class of large and costly practical trials. Over the past 6 years, the CER approach has gained broader support and substantial momentum. The congressionally authorized Patient-Centered Outcomes Research Institute (PCORI) funds a range of clinical effectiveness studies. The NIH Common Fund Health Care Systems Research Collaboratory project, co-led by NIMH, has supported CER trials in large health care delivery systems. The Center for Medicare and Medicaid Innovation, part of the Centers for Medicare and Medicaid Services, was established to answer practical questions about health care delivery, often via the support of CER-type trials. Further, the new NIH National Center for Advancing Translational Sciences has focused on CER across its 62 Clinical and Translational Science Centers. None of these various sources of support for CER, which in aggregate surpass a billion dollars per year, were present 6 years ago. This changes the NIMH role to partner rather than sole supporter of CER for mental health, with a responsibility for ensuring that these other sources of support include research on mental illnesses.

### **New Sources of Research Support and Collaboration**

The structure and function of the brain in health and illness has become an area of high interest for private as well as public research investment. Private, nonprofit organizations such as the Stanley Medical Research Institute, the Simons Foundation, the Allen Institute for Brain Science, the Brain and Behavior Research Foundation, and the Kavli Foundation, to name just a few, have each developed unique approaches to contribute to understanding the brain and mental illnesses. Over the past 6 years, private support for mental health research has soared with the formation of new institutes and the creation of new funding sources. From the researcher's perspective, science philanthropy provides almost 30 percent of the annual research funding in leading universities and has been growing at almost 5 percent annually.<sup>6</sup> Internationally, there is also increased investment in brain and mental health research, although this tends to be with public rather than private funding. National brain research projects have been launched in the European Union, China, Japan, Australia, and Israel. With private funding and global support increasing over the past 6 years, NIMH can look to new partnerships for funding, potentially leveraging new privately funded research programs.



## Citizen-Centered Science

A final and relatively new form of collaboration—citizen-centered science—holds considerable promise for revolutionizing the way biomedical research is conducted. Citizen-centered science builds solutions for research problems on a culture of data sharing and crowd sourcing. Whether through challenges for solving basic science problems or by empowering patients in clinical trials, new models have emerged over the past 6 years. Promising models and solutions for these challenges are being actively pursued by new citizen-science research partners, such as the Genetic Alliance, Patients-Like-Me, 23andMe, and Sage Bionetworks.<sup>7</sup>

## CROSS-CUTTING RESEARCH THEMES

With the changing ecosystem for neuroscience and mental health research, each of the Strategic Objectives of the 2008 Plan has evolved. Along with the specific changes in research objectives, several cross-cutting themes have emerged that are relevant to each of the Objectives. This section summarizes the major themes that, along with the changing landscape, motivated this Strategic Plan for Research.



### Transforming Diagnostics

The **Research Domain Criteria (RDoC)** Initiative—which began as Strategy 1.4 within SO1 in the 2008 Strategic Plan—has grown into a significant cross-cutting effort for the Institute. In contrast to current symptom-based diagnostic systems for mental illnesses, RDoC integrates many levels of information

(from genomics to social factors) for each patient to provide a precise characterization. RDoC frees clinical investigators from the current diagnostic categories and encourages basic scientists to identify molecular or neural mechanisms of specific domains of a mental function rather than creating models of diseases. Information from the RDoC project is now being aggregated into a common, comprehensive database—called RDoCdb—which will allow researchers to share and mine the results of NIMH-funded research.

### Accelerating Therapeutics

New tools and discoveries from genomics, neuroscience, and cognitive science have led to new ideas about treatment targets across mental illnesses. As industry has backed away from investing in research and development for new medications and payers have raised questions about the evidence base for nonpharmacological treatments, NIMH has begun shifting its clinical trials portfolio toward studies with defined targets and milestones. In contrast to previous studies that looked only for

statistical differences in efficacy, the Institute’s new experimental medicine approach seeks trials that will also reveal more about the mechanisms of disorders, serving as a foundation for better biomedical and psychosocial interventions.<sup>ix</sup>

### **Role of the Environment**

A decade of progress in genomics has emphasized the importance of the environment in the pathogenesis of mental illnesses. For disorders like PTSD, trauma is by definition a major factor. But even in psychiatric disorders in which genomic factors are substantial contributors, like schizophrenia, research has demonstrated the importance of environmental exposures. The list of environmental issues spans individual factors, such as early adversity and the microbiome, to social factors, such as poverty and neglect. While the tools for the exposome are not as precise as tools for the genome, the mechanisms by which environmental factors alter the development of brain and behavior can now be studied and will continue to be a rich area of investigation going forward in each of the Strategic Objectives.

### **Digital Enterprise**

The success of RDoC and many other initiatives at NIMH requires a new culture of open science with broad and rapid data sharing. In this era of big data, revolutionary changes in data acquisition have created profound challenges, from storing massive quantities of data, to harmonizing and integrating data collections, to translating data into better knowledge, to addressing the impact on privacy and confidentiality. The [National Database for Autism Research \(NDAR\)](#) is an example of harnessing data sharing for collaborative science. Looking forward, the NDAR approach to collaborative data sharing will continue to grow, for example, through the [National Database for Clinical Trials \(NDCT\)](#), which will collect individual-level data from NIMH-supported clinical trials, and through the [RDoCdb](#), which will collect data from relevant clinical studies. NIMH is committed to working with the scientific community to identify common data elements that can support the integration of data across studies and to support the broad sharing of data and the resources necessary to accelerate scientific progress.



<sup>ix</sup> Psychosocial interventions are interventions focused on, or relating to, the interaction of social factors, individual thought, and behavior.

## **Transforming the Trajectory of Mental Illnesses Through Preemptive Medicine**

Approximately 100,000 adolescents and young adults have a first episode of psychosis (FEP) each year in the United States.<sup>8</sup> The majority of people with serious mental illnesses, even those with psychosis, experience significant delays in seeking care—nearly 2 years, on average.<sup>9, 10</sup> Through a series of major initiatives, NIMH is striving to improve early identification of individuals at high risk for FEP, to reduce the period of untreated psychosis to less than 12 weeks, and to maximize recovery among persons in the earliest stages of psychotic illness. The NIMH Early Psychosis Prediction and Prevention (EP3) initiative seeks to accelerate research on detecting risk states for psychotic disorders with the aims of preempting onset of psychosis in high-risk individuals and ultimately reducing the incidence to well below 100,000 cases per year, reducing the duration of untreated psychosis in individuals experiencing FEP, and improving clinical and functional outcomes among persons in the earliest stages of serious mental illnesses.

### **Global Mental Health**

The challenges associated with mental illnesses are a global concern, and represent an opportunity to learn from, and with, other countries and other cultures. The rapidly increasing diversity of the U.S. population necessitates this global orientation. Worldwide, the distribution of morbidity associated with mental illnesses varies within and between countries. Within countries, disparities in mental health care and in the course and severity of illness occur along geographic and socioeconomic, as well as racial and ethnic, lines—as in the United States. Between countries, risk and protective factors, illness trajectories, and availability of quality care vary considerably. Addressing these shared challenges enriches the scientific enterprise overall, and will help us to advance U.S. research and to improve mental health care both domestically and globally. Insights from collective experience, along with varied perspectives, will inform mental health services and will help to find contextually appropriate solutions to reduce the burden of mental illnesses.

### **Mental Health Disparities**

In U.S. mental health care, we see striking differences in illness prevalence and outcomes based on sex, gender, age, race, ethnicity, and geography. NIMH research needs to include adequate numbers of men and women and members of diverse racial/ethnic groups in studies—from genomics to services research—in order to detect and mitigate these disparities. In addition, studies of diverse populations can contribute to our understanding of risks for mental illness, responsiveness to prevention and treatment interventions, and access to and engagement in care.



Specifically, research on sex, gender, age, racial, and ethnic differences related to mental disorders will provide information essential to the development of precision medicine and personalized interventions.

## Partnerships

To achieve our public health mission, NIMH must work with external stakeholders who are also committed to the prevention, recovery, and cure of mental illnesses. By utilizing existing partnerships with many stakeholders—whether they are patients, their families, service providers, advocacy groups, sister agencies in the U.S. Department of Health and Human Services, private partners (both domestic and international), or others—NIMH can efficiently leverage our collective investments and research infrastructure, as well as help evaluate and learn from stakeholders' experiences. In addition, rigorous collaboration, communication, and coordination between NIMH and its many stakeholders will lead to a quicker uptake of effective practices and programs. NIMH also seeks to develop new research partnerships, especially where there may be opportunities to harness developments in the fast-moving area of citizen-driven science. In all these ways, NIMH intends to maximize the impact of its research investments on the lives and outcomes of people with mental illnesses.

## Investing in the Future

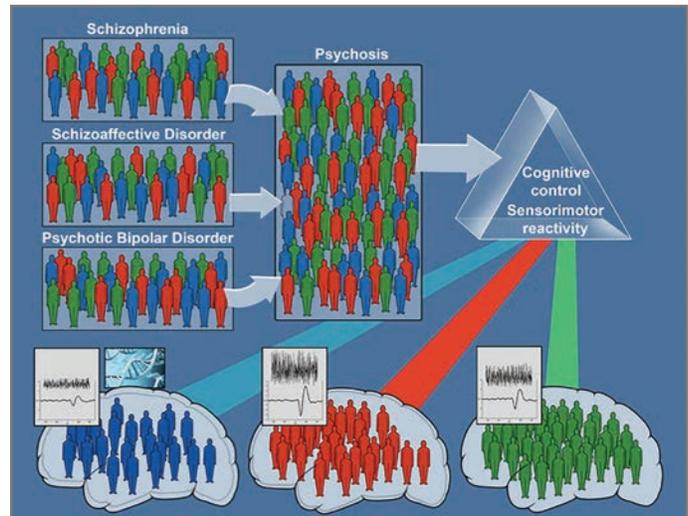
Finally, all research advances rest on our ability to support and train future generations of mental health researchers. NIMH will build on the guidance found in the National Advisory Mental Health Council Workgroup on Research Training report, *Investing in the Future*,<sup>x</sup> to foster future generations of research scientists. Just as the research enterprise must adapt to a changing ecosystem, so must the training of future research scientists. Future research scientists must be prepared to use expanded biological, translational, clinical, and services skill sets to advance and transform the research enterprise across traditional academic boundaries. While the specific goals of NIMH-supported training were not included as part of this research plan, NIMH is committed to working with the scientific community to better understand future workforce needs and to inspire the next generation of committed scientists.



<sup>x</sup> For the *Investing in the Future* report, see: [http://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/investing-in-the-future\\_42525.pdf](http://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/investing-in-the-future_42525.pdf) [PDF - 1 MB].

## What Is RDoC?

NIMH launched the Research Domain Criteria (RDoC) project as part of the 2008 NIMH Strategic Plan's call for new ways of classifying mental illnesses—based on dimensions of observable behavior and neurobiological measures. Much has happened to the RDoC concept since its inception in 2009. Through a series of workshops, NIMH developed a matrix of units of analysis (from molecules to self-report) for several domains (cognitive, positive valence, negative valence, social processes, arousal and regulatory systems)—all examined in a context emphasizing developmental trajectories and the individual's interactions with his or her environment. The RDoC matrix has become a framework for organizing our research efforts, as it frees scientists from traditional categories that have proven to be heterogeneous. For example, recent studies of psychosis (see BSNIP figure),<sup>11</sup> mood disorders, and attention-deficit hyperactivity disorder demonstrate new ways to group individuals based on genomics, cognitive dimensions, physiological traits, or imaging findings. RDoC assumes these new clusters will not only provide more precise diagnostic categories, they will also produce better guidance to treatment and ultimately lead to better outcomes. Will RDoC become a diagnostic system like the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases? No, RDoC is an experiment to determine if a diagnostic approach based on biology, behavior, and context will be useful for mental disorders. This experiment will involve an information commons with participation from scientists, providers, patients, and families. And if successful, we hope that RDoC will inform the diagnostic systems of the future.



The Bipolar Schizophrenia Network on Intermediate Phenotypes (BSNIP) project is an example consistent with the RDoC project. In BSNIP, individuals were pooled across multiple diagnostic groups in the psychosis spectrum without regard to traditional diagnoses (e.g., “bipolar I” or “schizophrenia”). The investigators studied a range of variables across levels of analysis and used statistical techniques to identify clusters of individuals based on patterns in the data that were independent of traditional diagnoses. These “biotypes” may have greater biological validity and potentially better clinical predictability than diagnostic categories limited to observable symptoms.

Source: Carol Tamminga, M.D., University of Texas Southwestern Medical Center

“BSNIP initiated a study across the dimension of psychosis to develop biomarkers for our diagnoses. The RDoC concept gave us the confidence to eschew these traditional diagnoses and seek biological bases for serious mental illness with psychosis. RDoC will stimulate the field to the kind of novel conceptualizations that will generate progress for psychiatry.”

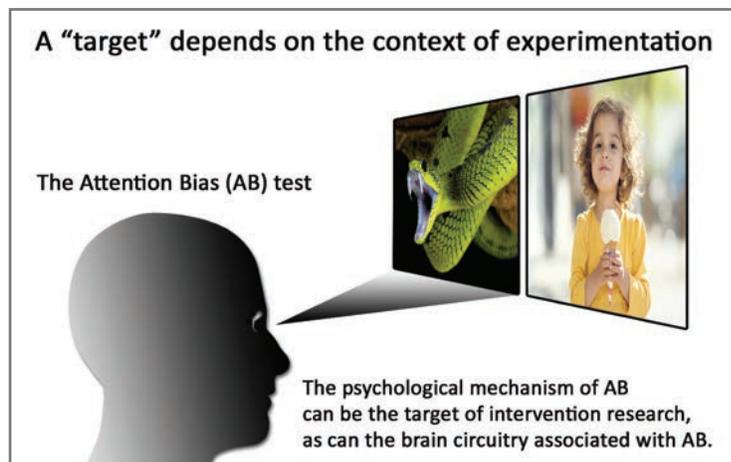
Carol Tamminga, M.D.  
University of Texas Southwestern Medical Center

# What Is a Target?

The term “target” refers to a hypothesized mechanism of action and its ability to modify disease, behavior, or functional outcomes. Given the broad range of science that NIMH funds, “target” can refer not only to mechanisms within an individual patient, but also to external factors that impact mental health outcomes such as the attitudes and behaviors of health care providers, the influence of peers or family members, or characteristics of health care systems. Thus, targets can range from molecular- and circuit-level mechanisms proposed for pharmacologic agents, to neural systems, cognitive processes for psychosocial behaviors, or provider decision making, to organizational behaviors that are thought to underlie the benefits of a psychosocial- or service-level intervention.

The basis of experimental medicine is the assumption that modification of the target will result in improvement of symptoms, behavior, or functional outcomes. A good target at the individual level should be strongly associated with a clinical symptom or functional deficit, and evidence should strongly suggest that the target

impacts a psychological or biological pathway through which a clinical or functional benefit occurs (see figure). In the case of services interventions, an intervention may target the patient (e.g., adherence), the provider (e.g., fidelity in the delivery of research-supported pharmacologic or psychosocial interventions), or the system/organization (e.g., organization climate, readiness to adopt evidence-based practices) in the service of improving access, engagement, or quality of mental health services. The demonstrated success of the experimental medicine approach in other areas of medicine, such as cancer and diabetes, has depended on the research community’s ability to identify and demonstrate engagement of targets. This will be equally true for mental health research taking place at all scales, from individual research projects to large-scale trials.



*Children and adults with anxiety often preferentially visually attend (also known as attention bias) to a threatening image (snake image on left). Researchers are focusing on attention bias as the “target” of promising treatments for anxiety disorders.<sup>12</sup> Attention Bias Modification Treatment trains individuals to more quickly disengage from threatening situations and, in doing so, alleviates anxiety stemming from the threat.*

*Investigators are also pursuing other approaches to assess and study attention bias. Using brain imaging, it is now known that attention bias is associated with abnormal function in a specific brain region called the ventral lateral cortex.<sup>13</sup> Abnormal functioning within this region may be the reason why individuals have difficulty directing attention to useful behaviors following a threatening situation. In this context, the ventral lateral cortex can be considered a “target” for the development of novel anxiety-disorder treatments that augment attention control of individuals toward useful tasks.*

*Source: Image created by NIMH.*

## ACCOMPLISHING THE MISSION

The ecosystem in which NIMH works to accomplish its mission is rapidly changing. There are both new and existing cross-cutting interests that will influence the direction of mental health research as we move forward. Amid this sea of change, what future does NIMH envision, and how will this shape our journey?

The following sections of the Strategic Plan for Research outline at the highest level how NIMH proposes to confront the many challenges ahead as we envision a future where mental illnesses are prevented or cured. NIMH encourages the submission of investigator-initiated applications and responses to Requests for Applications aligned with this Plan. To foster the most germane applications, NIMH recognizes the research community's need for more detailed guidance on specifics encompassed by the strategies in this Plan. Our [Strategic Research Priorities](#)<sup>xi</sup> describe areas of specific interest. The information within the Strategic Research Priorities pages on the NIMH website will be updated periodically to represent the most current interests of NIMH. We encourage you to check the site for the most recent insights on research needs.

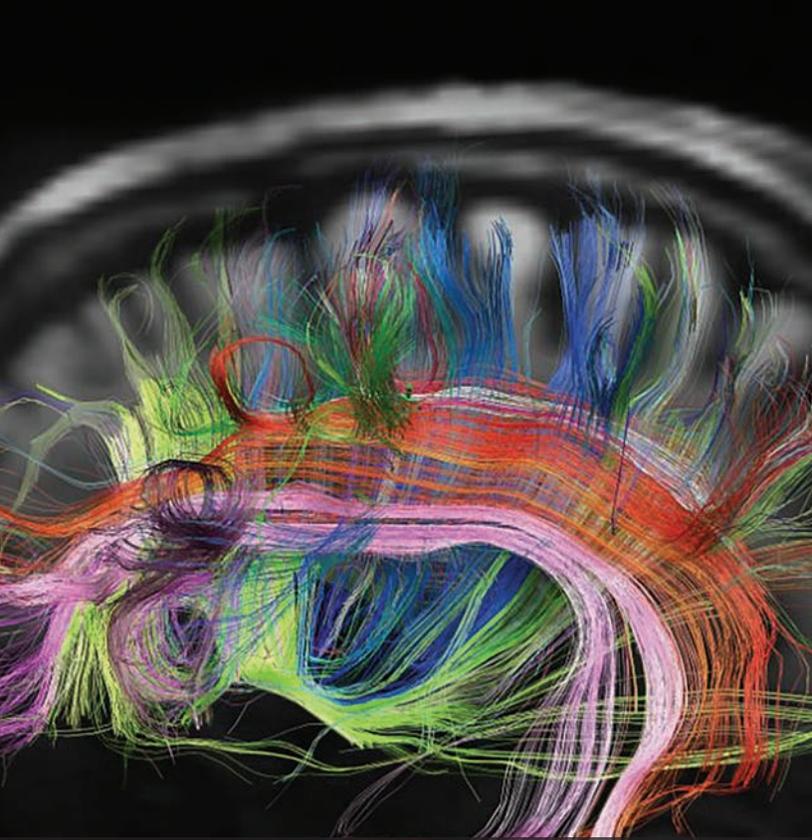
## VISION

NIMH envisions a world in which mental illnesses are prevented and cured.

## MISSION

To transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure.

<sup>xi</sup> For the Strategic Research Priorities, see: <http://www.nimh.nih.gov/research-priorities/strategic-objectives/index.shtml>.



**Strategic Objective 1:**

Define the Mechanisms of Complex Behaviors



**Strategic Objective 2:**

Chart Mental Illness Trajectories



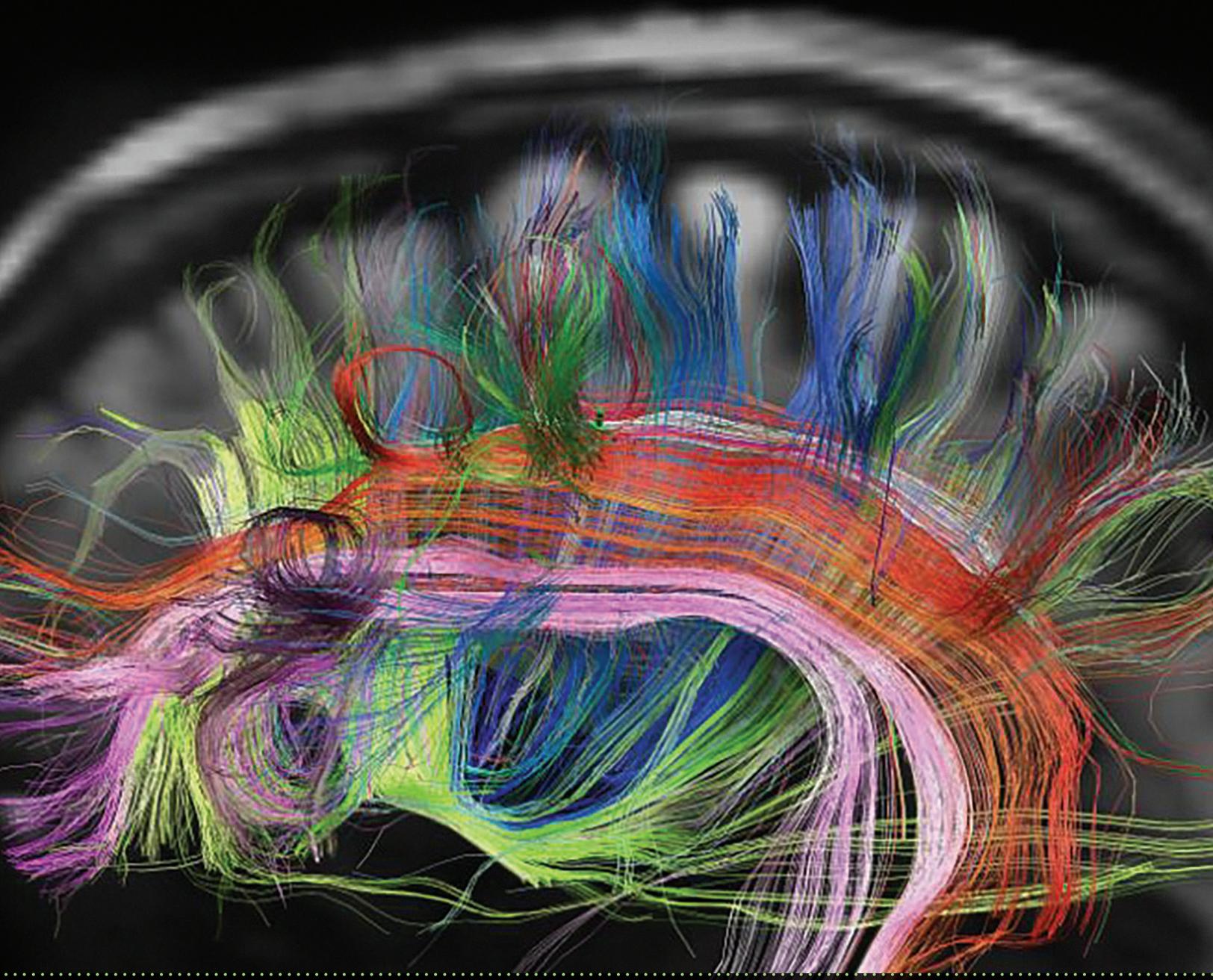
**Strategic Objective 3:**

Strive for Prevention and Cures



**Strategic Objective 4:**

Strengthen the Public Health Impact



**STRATEGIC OBJECTIVE 1** focuses on the basic science required for understanding mental illnesses. This objective serves as a foundation for a research continuum leading to better interventions and services.

## Strategic Objective 1: Define the Mechanisms of Complex Behaviors

The basic science of mental illnesses has seen extraordinary progress over the past 6 years. The genomics revolution, fueled by rapid sequencing, has revealed complex genetic variation associated with mental illnesses. Epigenomics has demonstrated the molecular mechanisms by which environmental factors like stress and social experience influence behavior. In neuroscience, new tools such as optogenetics<sup>xii</sup> and DREADDs<sup>xiii</sup> have enabled precise mapping and manipulation of brain circuits in nonhuman animals. New techniques have improved the resolution of structural and functional imaging in humans, and sensor technologies are transforming the study of behavior. Together, these new tools, techniques, and technologies can help us understand the still mysterious links between genes, experience, brain, and behavior.

The human brain is thought to have close to 86 billion neurons, each making on average about 10,000 connections. Approximately 100,000 miles of axons serve as information highways between neurons.<sup>14</sup> Although this complexity is formidable, new reference atlases that have emerged from the [Human Connectome Project](#)<sup>xiv</sup> and the [BrainSpan Project](#)<sup>xv</sup> provide unprecedented resources for mapping genes and pathways in the human brain. In the next 5 years, we expect a new generation of tools and technologies to be developed via the [BRAIN Initiative](#).<sup>xvi</sup> These tools will help create a detailed map of the circuits involved in complex behavior, including those associated with mental illnesses.

The questions we are asking include: What are the neural bases of perception, cognition, motivation, and social behavior? How do these aspects of mental function—which represent how we perceive, interpret, react to, and interact with the world—become altered in mental illnesses? The answers will come from discovery-based and hypothesis-testing studies examining the biological mechanisms underlying

<sup>xii</sup> Optogenetics allows scientists to turn brain circuits on and off in living animals and view the resulting behavioral changes.

<sup>xiii</sup> “**Designer Receptors Exclusively Activated by Designer Drugs.**”

<sup>xiv</sup> For information about the Human Connectome Project, see: <http://www.humanconnectomeproject.org/>.

<sup>xv</sup> For information about the BrainSpan Atlas, see: <http://www.brainspan.org/>.

<sup>xvi</sup> For more information about the NIH BRAIN Initiative, see: <http://braininitiative.nih.gov/>.

the regulation and dysregulation of mental processes. How these mechanisms emerge across development and among diverse populations; how they differ based on sex, gender, age, race, and ethnicity; how they change with experience (e.g., trauma or poverty); and, how they are influenced by environmental factors (e.g., cultural, economic, geographical, social, technological) are all critical questions for research. A more refined understanding of the molecules, genes, cells, and neural circuits underlying complex behaviors will be the starting point for the interventions of tomorrow.



Over the past 6 years, large, replicated genomic studies have revealed many common and rare variants associated with the most heritable conditions (e.g., schizophrenia, bipolar disorder, autism). We have gone from few clues to many. However, we still cannot explain the root cause(s) of mental illnesses. The task now is to sort through the complex patterns of genomic variation to define and elucidate how these variations confer risk. This strategy should not only identify critical pathways and circuits but potential new therapeutic targets. Nongenetic factors (e.g., environment, experience, the microbiome, to name just a few) have also been shown to increase the risk of mental illnesses. How does the interplay of genetic and environmental factors influence the development of mental illnesses? By understanding genomic, epigenomic, and other non-genomic factors and their interplay, we can begin to explain how our brain generates adaptive and maladaptive behaviors—predicting, interpreting, and responding to a complex world.

While genomic research has taught us that individual variation is a source of risk and resilience for illnesses, the study of brain circuits is still focused more on group averages than on individual differences. To address the range of individual variation in brain circuits, the Human Connectome Project is providing a reference atlas of neuronal connectivity—or a connectome—of 1,200 healthy brains. Moving forward from this baseline atlas, we will need to explore the details of individual differences in circuitry across diverse populations. We know little about the range of variation in connectomes across development, and even less about the potentially altered connectomes underlying mental illnesses from birth to the onset of illness. Imagine the questions we could answer, and the possibilities for new interventions, if we could define connectomes for mental illnesses that span development. When do structural and functional differences begin to manifest? How do differences in circuitry relate to differences in function? When is it best to intervene to correct deficits, and how do we intervene? To understand changes in neural structure and function related to mental illnesses, we must apply and build upon the research tools and technologies that we have in hand to begin to elucidate connectomes for mental illnesses, extending current group studies for use in individuals.

To improve our understanding of the structure and function of the brain in both health and illness and lay the foundation for future interventions, NIMH will employ the following strategies:

## STRATEGY 1.1: DESCRIBE THE MOLECULES, CELLS, AND NEURAL CIRCUITS ASSOCIATED WITH COMPLEX BEHAVIORS

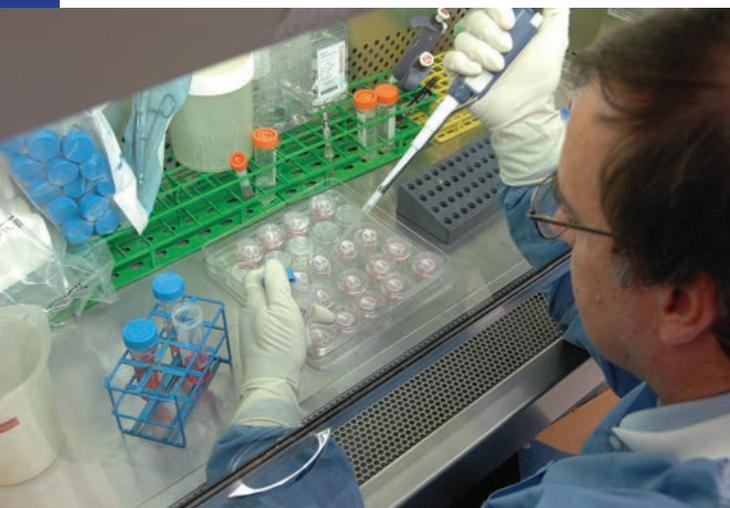
To unravel the mechanisms that lead to mental illnesses and target novel treatments to those mechanisms, more comprehensive descriptions of the molecules, cells, and circuits associated with typical and atypical behavior are necessary. What classes of neurons and glia are involved in a given aspect of mental function? Which brain regions contribute to a single thought or action, and how are these regions interconnected? These questions will be answered by defining the cellular components of circuits, including their molecular properties and anatomical connections. New tools and techniques that



span biological scales—from single-cell analysis, to macro-electrode arrays, to systems-level brain imaging—are needed to address these questions. We still have little understanding of the neural basis for changes in structure or activity observed in human brain imaging. Most structural changes have not been validated with post-mortem anatomy, and most functional changes have not been validated with *in vivo* physiology. Progress on this strategy will reveal how the brain is organized across the molecular, cellular, and systems levels, and will provide a foundation for understanding mental illnesses. To implement this strategy, NIMH will support research to:

- Determine the molecular, cellular, and systems components underlying brain connectivity and dynamic patterns of brain activity using model systems, stem cells, and human studies.
- Identify the mechanisms responsible for establishing and maintaining circuits.
- Identify and validate novel assays to quantify changes in the activity of molecules, cells, and circuits.
- Elucidate the basic biology linking changes in molecular-, cellular-, and circuit-based targets to alterations in complex behaviors.

## STRATEGY 1.2: IDENTIFY THE GENOMIC AND NON-GENOMIC FACTORS ASSOCIATED WITH MENTAL ILLNESSES



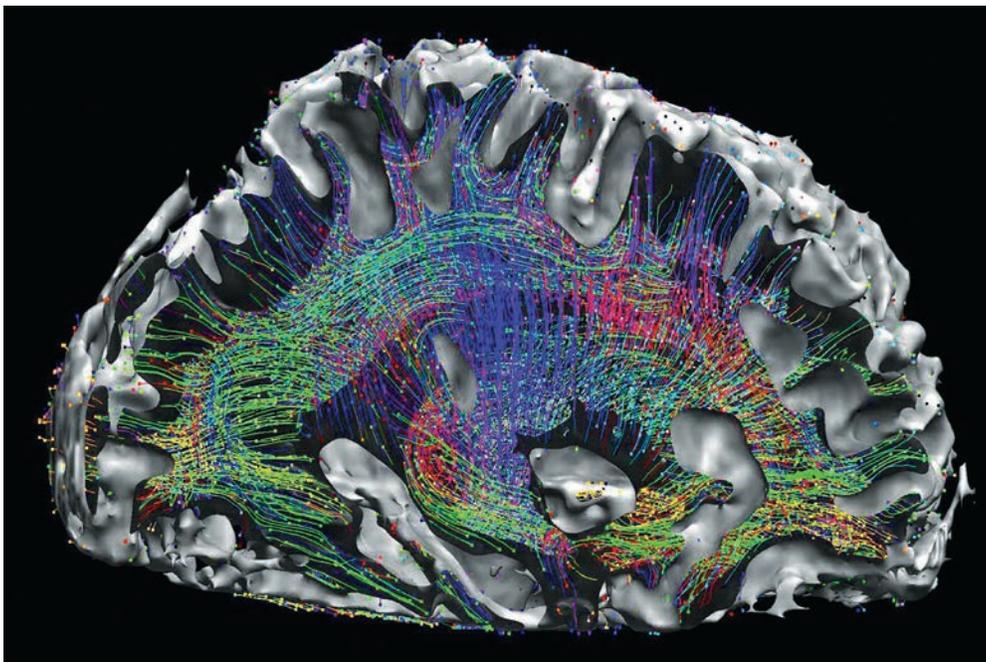
Understanding the risk of developing a mental illness requires examination of genomic, epigenomic, and other factors such as the environment and experience across diverse populations. It is crucial to describe how these factors jointly influence the risk of developing mental illnesses; this knowledge provides a foundation for early prediction and preventive interventions. Novel study designs, genotyping technologies, and innovative statistical and bioinformatic methods will augment the analysis and interpretation of observed gene-environment interplay and will speed the transition of this

knowledge to practice. Progress in these areas will broaden our understanding of the precise factors at the root of mental illnesses. To implement this strategy, NIMH will support research to:

- Define genomic variations associated with mental illnesses and determine the biological consequences of these variations.
- Define the molecular mechanisms that determine how experience has enduring effects on gene expression, brain function, and behavior.
- Delineate environmental and biological factors altering genomic risk for mental illnesses.
- Develop analytical tools for multi-scale data integration.

### STRATEGY 1.3: MAP THE CONNECTOMES FOR MENTAL ILLNESSES

Most of what we currently know about the human brain connectome comes from studying healthy individuals. To understand changes in neural structure and function related to mental illnesses, we must apply the research tools and technologies we



Source: *Cristophe Lenglet, Ph.D., Center for Magnetic Resonance Research, Department of Radiology, University of Minnesota Medical School*

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have in hand to characterize the connectomes for mental illnesses. It is becoming increasingly possible to map both local and distant connections in the brain, enabling an understanding of the relationships between neuronal structure and function at the systems level. To have comprehensive connectomes for mental illnesses, we must extend existing structural and functional mapping to the cellular level. The BRAIN Initiative will bring us improved technologies—technologies that are faster, less expensive, and scalable for anatomic reconstruction of neural circuits at all biological scales—and innovative tools, for example, molecular markers for synapses, tracers for identifying circuit inputs and outputs, and novel microscopy techniques for reconstruction of brain circuits. Until then, the application of existing tools and technologies will continue the transformation of how we visualize structural and functional differences in the brain connectomes for mental illnesses. To implement this strategy, NIMH will support research to:

- Identify cells and brain networks that contribute to various aspects of mental function and dysfunction, such as cognition, emotion, and social behavior.
- Determine how changes in the physiological properties of molecules, cells, and circuits contribute to mental illnesses.
- Develop biomarkers of impaired neural function in humans at the level of molecules, cells, and circuits.
- Develop innovative technologies, as well as new pharmacological and genetic tools, to interrogate and modulate the signaling pathways and circuits altered by mental illnesses.

# Disease-in-a-Dish

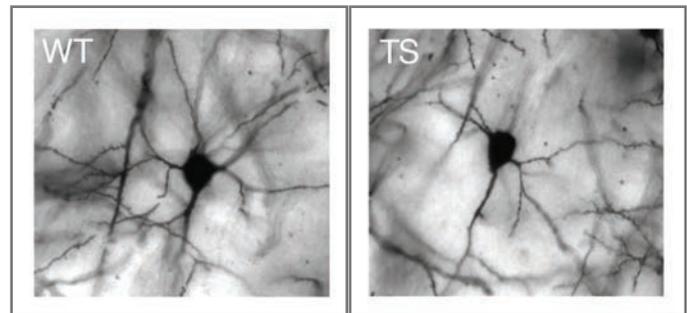
The developmental events within the brain that lead to heightened risk for illnesses such as autism and schizophrenia occur long before symptoms appear. How might we learn what these events are, and how to prevent and treat them? A technology called induced pluripotent stem cells (iPSC) holds promise. The iPSC process first alters a person's skin cells to resemble the stem cells from which they were originally derived. These cells are then induced to differentiate into neurons or glial cells bearing the person's same genetic signature, thus mimicking an affected brain cell—a veritable disease in a dish! Potentially, researchers can discover the neurodevelopmental secrets of that person's illness by experimenting with the cells growing in culture. In the future of precision medicine, this information might even lead to engineering a specific treatment for a person's unique illness. In the meantime, the iPSC technique has become a boon to discovery.

## My Neurons—Fast!

Until recently, methods used to coax induced stem cells to differentiate into neurons were comparatively slow and inefficient, resulting in hobbled neurons with diminished capacity to form connections, or synapses. Nobel Laureate [Thomas Südhof, M.D.](#), of Stanford University and his colleagues have developed a shortcut to rapidly convert induced human stem cells into viable neurons. The breakthrough method opens the way to large-scale production of induced human neurons for studying the causes of mental illnesses, screening potential treatments, and developing regenerative therapies. This new method readily yields functional, pure neurons in less than 2 weeks—with nearly 100 percent success. To understand how these neurons function, they need to be integrated into a system of neurons—a neural circuit. Researchers are now growing circuits in cultures and transplanting the new human neurons into mouse brains, promising rapid turnaround between new knowledge of mechanisms and translation into practical applications. The new method is based on tweaking a single pivotal regulator of gene expression.<sup>15</sup> Using this iPSC approach, [Ricardo Dolmetsch, Ph.D.](#), and colleagues at Stanford University discovered the molecular workings of Timothy syndrome and another genetic syndrome related to autism by pinpointing the molecular defects and correcting them in cultured neurons grown from patients' own skin cells.<sup>16</sup>

“The brain works by neurons communicating via synapses. We'd like to understand how synapse communication leads to learning on a larger scale. How are the specific connections established? How do they form? And what happens in schizophrenia and autism when these connections are compromised?”

*Thomas Südhof, M.D.  
Stanford University*



*In a mouse model of Timothy syndrome, branched extensions of neurons, called dendrites, failed to develop normally in animals with the mutation (right) versus control animals (left).*

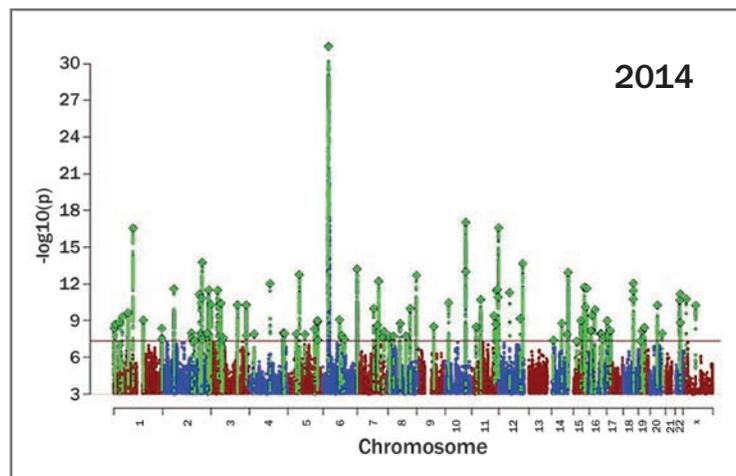
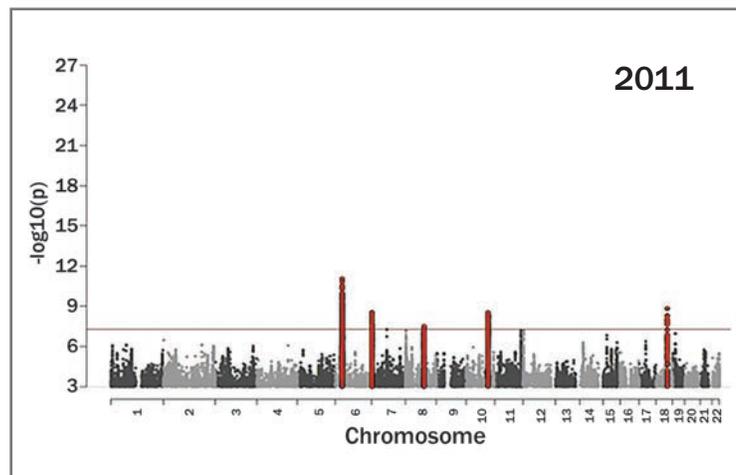
*Source: Ricardo Dolmetsch, Ph.D., Stanford University*

# Skyline Drivers

The skyline-like pattern created by graphing the genes implicated in schizophrenia grew dramatically over the past few years, with the advent of more statistically powerful studies.<sup>17,18</sup> Now the challenge is to discover which of these genetic changes alter brain circuitry. To find out how a gene works in the brain, scientists selectively silence that gene in a living neuron. A new genetic engineering technique called CRISPR,<sup>xvii</sup> adapted for neuroscience by Feng Zhang, Ph.D., and colleagues at the Massachusetts Institute of Technology, offers a way to readily and precisely edit DNA—to fix “typos” in the genomes of living cells by adding or deleting genes using the Cas9 complex. A DNA snipping enzyme borrowed from bacterial antiviral defenses, teamed with a “programmable” RNA guidance system, becomes an exquisitely specific missile that can precisely target any site in the genome. A suspect gene variant—such as one of the more than 100 linked to schizophrenia that are driving the skyline in the bottom graph—could potentially be inserted into stem cells and grown into neurons—via “disease-in-a-dish” technology (see Highlight, page 27)—to study the cellular machinery of the disease process. The CRISPR technology could someday evolve into a therapeutic tool for treating such genetically influenced mental illnesses.<sup>19</sup>

“We’ve come to view the Cas9 complex as the ultimate guided missile that we can use to target precise sites in the genome.”

Feng Zhang, Ph.D.  
Massachusetts Institute of Technology



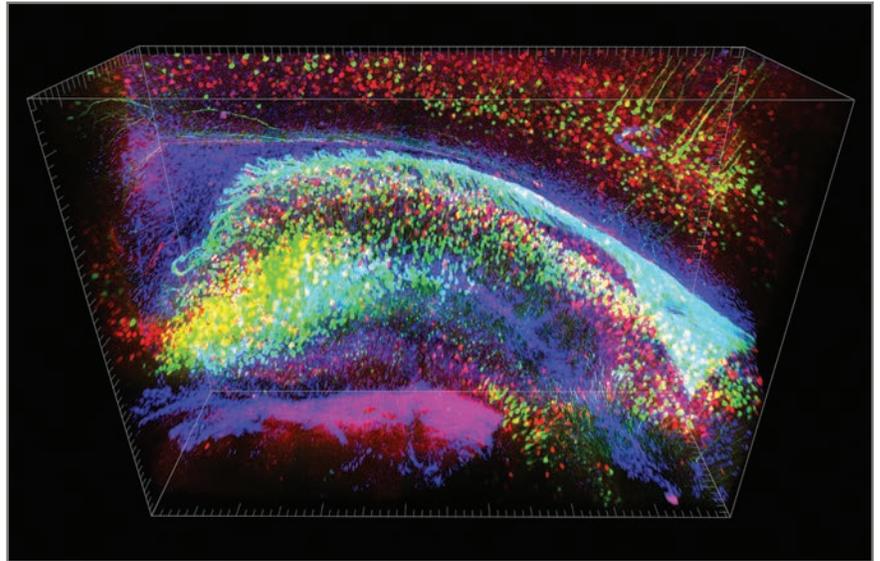
The “skyline”—Manhattan plot graph of genetic variation associated with schizophrenia—has risen dramatically over the past few years, thanks to the enhanced ability to detect subtle effects of common gene variants that comes with larger sample sizes. Bars that rise above the red line indicate chromosomal sites that confer risk.

Source: Psychiatric Genomics Consortium

<sup>xvii</sup> “Clustered Regularly InterSpaced Palindromic Repeats.”

## Slicing Optional

Until recently, researchers studying the brain's fine structure and connections faced tradeoffs. To probe deeply and with high enough resolution to analyze cells, molecules, and genes, researchers had to slice brain tissue into thin sections—making it hard to relate fine structure to more macro-level information about wiring and circuitry. Enter Karl Deisseroth, M.D., Ph.D., of Stanford University and colleagues. By replacing the fat that normally holds the brain's working components in place with a clear gel, these researchers made the brain's normally opaque and impenetrable tissue transparent and permeable. This opens the intact post-mortem brain to the same kind of chemical, genetic, and optical analyses that used to require slicing—while preserving the brain's 3-D structure and the integrity of its circuitry and other biological machinery. The technique—CLARITY<sup>xviii</sup>—promises to transform the way scientists study the brain's anatomy and how disease changes it.<sup>20</sup>



CLARITY provided this 3-D view showing a thick slice of a mouse brain's memory hub, or hippocampus. It reveals a few different types of cells: projecting neurons (green), connecting interneurons (red), and layers of support cells, or glia (blue). Conventional 2-D methods require that brain tissue be thinly sliced, sacrificing the ability to analyze such intact components in relation to each other.

“CLARITY will help support integrative understanding of large-scale, intact biological systems. It provides access to subcellular proteins and molecules, while preserving the continuity of intact neuronal structures such as long-range circuit projections, local circuit wiring, and cellular spatial relationships.”

Karl Deisseroth, M.D., Ph.D.  
Stanford University

<sup>xviii</sup> “Clear Lipid-exchanged Anatomically Rigid Imaging/immunostaining-compatible Tissue hYdrogel.”



STRATEGIC OBJECTIVE 2 focuses on the crucial component of development, elucidating how brain and behavior change across the lifespan in health and illness.

## Strategic Objective 2: Chart Mental Illness Trajectories to Determine When, Where, and How to Intervene

In the past, we viewed mental illnesses as chronic conditions defined by their symptoms. However, based on our understanding of brain disorders, it seems likely that manifest mental illnesses are the late signs of changes in brain circuits and subtle disruptions in behavior and cognition that begin years earlier. These early abnormalities may influence the course of subsequent brain and behavioral development and establish a trajectory of mental illness.

Development is not a uniform, linear process. Rates of developmental change vary considerably across brain regions. For example, the regions of the adolescent brain involved in emotional responses are fully active, or even more active than in adults, while those areas involved in keeping emotional, impulsive responses in check are still reaching maturity. Moreover, the brain does not reach full maturity until well past 20 years of age. The dynamic nature of development and the observation that most mental illnesses emerge during the first two decades of life prompt critical questions: What are the earliest markers or signs that distinguish typical from atypical brain development? How do these markers or signs differ in meaningful ways across individuals and diverse populations (e.g., by sex, gender, age, race, ethnicity) and varied environmental (e.g., cultural, economic, geographical, social, technological) or experiential exposures? How can we intervene early to prevent the development of mental illnesses?

With the advent of more powerful and precise imaging technology and analysis methods, scientists have the tools to track brain and behavioral development. Concomitantly, our ability to understand the complexities of these processes in association with mental illnesses is growing. For example, studies have demonstrated that the genes and proteins expressed in the fetal and postnatal brain are so radically different that one could consider the fetal and postnatal brains as different organs with different functions.<sup>21,22</sup> Furthermore, increasing evidence has linked the trajectory of brain development with the



emergence of symptoms of mental illness in early life, such as psychosis in late adolescence or autism in very early childhood.



Developing a comprehensive picture of typical and atypical brain and behavioral development across the lifespan (conception to late life) and in diverse populations will help tell us when, where, and how to intervene. A focus on the early, presymptomatic phase of a mental illness is critical, as this may provide the best opportunity to identify individuals at highest risk and intervene at the earliest possible time. It will also be essential to identify and characterize sensitive periods across the full lifespan—that is, identify discrete time periods during which the impact of experience is particularly strong. Progress here

will allow us to know the points in time during which the brain is most sensitive to intervention and the underlying molecular-, cellular-, and system-level mechanisms responsible for this sensitivity. For the person with or at risk for a mental illness, findings from this research could lead to earlier diagnosis, earlier and more effective preventive and therapeutic interventions, and, ultimately, an improved outcome.

Our ability to prevent and treat mental illnesses and gauge the effectiveness of interventions depends on the identification of valid biomarkers and behavioral indicators; these tell us who is at risk, when development is going awry, or when an intervention is restoring function. To do this, we must increase our knowledge of the mechanisms through which multiple and interacting risk and protective factors operate. Knowledge of these risk and protective factors will provide the basis on which to develop novel clinical tools and effective interventions.

To better understand the progression of mental illnesses and lay the foundation for predicting outcomes and preemptive interventions, NIMH will employ the following strategies:

## STRATEGY 2.1: CHARACTERIZE THE DEVELOPMENTAL TRAJECTORIES OF BRAIN MATURATION AND DIMENSIONS OF BEHAVIOR TO UNDERSTAND THE ROOTS OF MENTAL ILLNESSES ACROSS DIVERSE POPULATIONS

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Investigating the interdependence and functional development of simultaneously maturing—yet unevenly progressing—systems and competencies will break new ground in understanding the development of mental illnesses. To understand what factors influence development and the risk for mental illnesses across diverse

populations, we must create a comprehensive, cross-lifespan map of trajectories (i.e., growth curves) of typical and atypical brain, cognitive, and behavioral development. Basic and translational research studies that describe the behavioral maturation and associated molecular, cellular, and circuit-level changes that occur over a lifespan are needed to create this map. To implement this strategy, NIMH will support research to:

- Characterize developmental processes across biological and behavioral domains of analysis that give rise to mental illnesses throughout the lifespan.
- Identify sensitive periods for typical and atypical mental health trajectories.
- Determine modifiers of maturational and illness trajectories, emphasizing periods of sensitivity to perturbation and/or potential for intervention.



## STRATEGY 2.2: IDENTIFY CLINICALLY USEFUL BIOMARKERS AND BEHAVIORAL INDICATORS THAT PREDICT CHANGE ACROSS THE TRAJECTORY OF ILLNESS

The best time to address a mental illness is before the appearance of symptoms that disrupt daily life. Preemptive interventions will rely on biomarkers that give health care providers the ability to predict the onset of illness for individuals, not just populations, at risk. To realize this, research must identify biomarkers and behavioral indicators with high predictive value, as early in the course of illness development as possible. Imagine a world where a straightforward set of physiological and/or cognitive tests indicates with high sensitivity and specificity an individual's risk for developing a mental illness, and points to an effective tailored intervention. To ensure this future, we must work today to identify markers of illness progression at molecular, cellular, circuit, and behavioral levels. To implement this strategy, NIMH will support research to:

- Identify early biological and environmental risk and protective factors and their underlying mechanisms to serve as novel intervention targets.
- Develop biomarkers and assessment tools to predict illness onset, course, and intervention response across diverse populations.



# Beautiful Convolutions

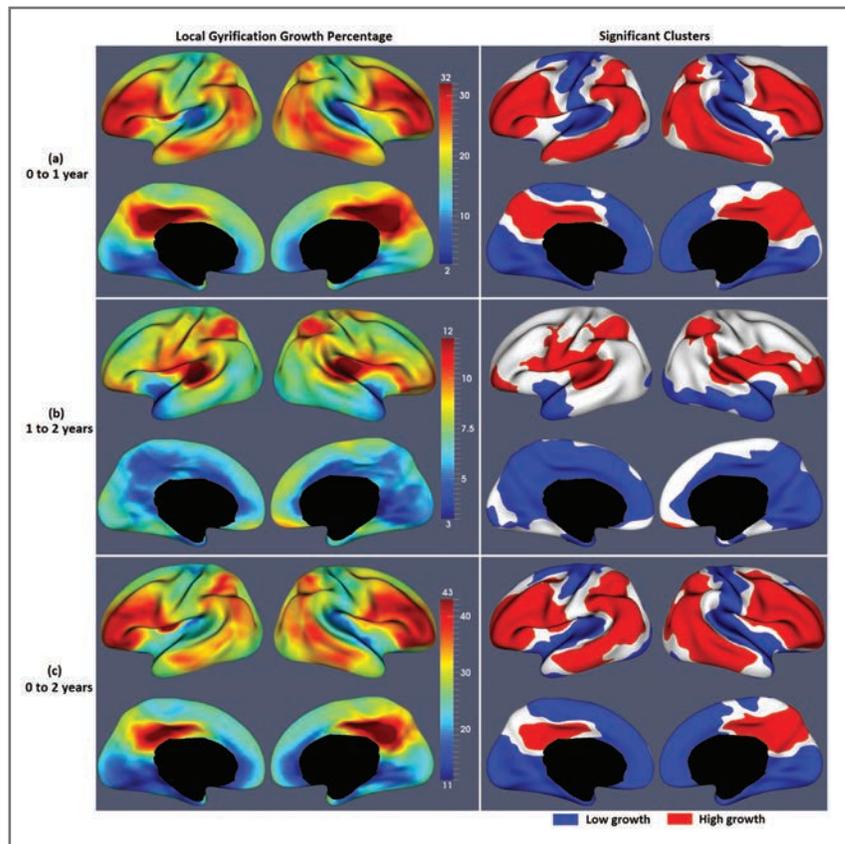
Several lines of evidence suggest that the origins of mental illnesses are likely in developmental processes taking place years before symptoms emerge. Researchers are working to understand the early maturation of the brain and how disruptions in development in early life contribute to later mental illness.

During the third trimester, the cerebral cortex—the outermost brain region and home to higher-order functions, including cognition—loses its smooth appearance and folds into complex grooves and wrinkles, during a developmental process called gyrification. Although the most dramatic brain growth takes place during the first years of life, previous studies were only able to provide information on the process of gyrification in school-age children and adolescents—not infants.

A group of researchers at the University of North Carolina at Chapel Hill recently developed a magnetic resonance imaging (MRI) approach that makes it possible to track gyrification in healthy infants.

These researchers found marked regional

differences in cortical development in infants' brains. High-growth regions were located in the association cortex, an area of the cerebral cortex that is involved in higher-order processes such as cognition, and low-growth regions were located in the sensorimotor, auditory, and visual cortices.<sup>23</sup> Previous work showed that between early childhood and adulthood, the growth of the cortex is not uniform, with areas involved in higher-order function expanding very rapidly.<sup>24</sup> This study provides a more comprehensive picture of how much asymmetric growth occurs very early in life. Such differences in growth rates across the brain may inform our understanding of mental illnesses, as researchers previously observed abnormal gyrification patterns in several neurodevelopmental illnesses, such as schizophrenia, autism spectrum disorder, and Williams syndrome. Insights from gyrification patterns may help us learn when and where to intervene to get developmental trajectories back on course.



*Dramatic brain growth takes place during the first 2 years of life. Cortical folding, or gyrification, during this period has high-growth regions (red) and low-growth regions (blue). Research on gyrification will help to determine how disruptions in development in early life contribute to later mental illness.<sup>23</sup>*

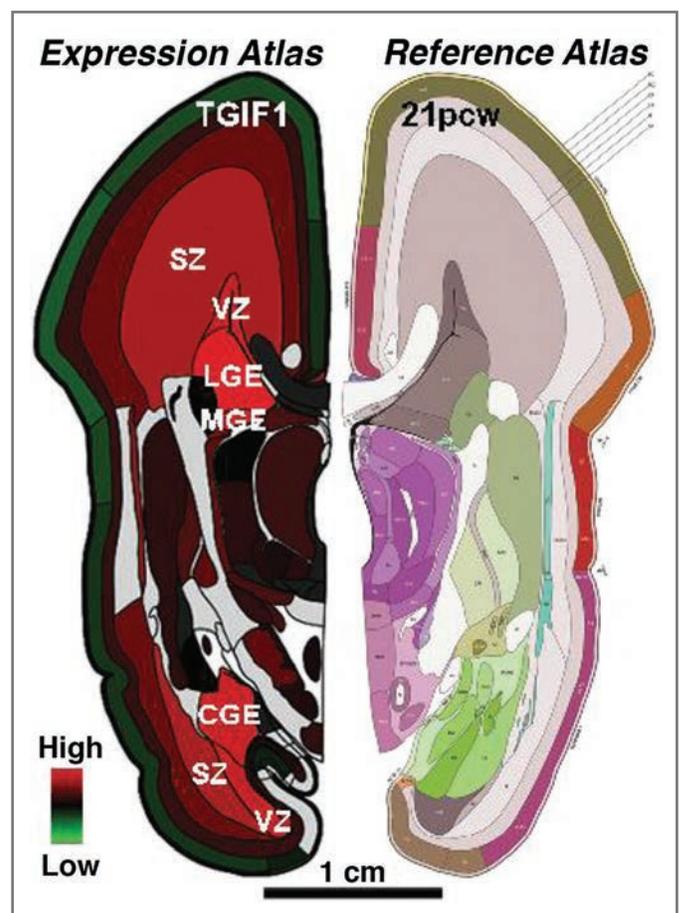
*Source: Dinggang Shen, Ph.D., University of North Carolina at Chapel Hill School of Medicine*

# GPS for the Brain? BrainSpan Atlas Offers Clues to Mental Illnesses

Technologies have come a long way in mapping the trajectory of mental illnesses. Early efforts provided information on anatomical changes that occur over the course of development. In a step that has been hailed as providing a “GPS for the brain,” the BrainSpan Atlas of the Developing Brain, a partnership among the Allen Institute for Brain Science, Yale University, the University of Southern California, and NIMH—has created a comprehensive three-dimensional brain blueprint.<sup>25</sup> The Atlas details not only the anatomy of the brain’s underlying structures, but also exactly where and when particular genes are turned on and off during mid-pregnancy—a time during fetal brain development when slight variations can have significant long-term consequences, including heightened risk for autism or schizophrenia.<sup>26</sup> Knowledge of the location and time when a particular gene is turned on can help us understand how genes are disrupted in mental illnesses, providing important clues to future treatment targets and early interventions. The Atlas resources are freely available to the public on the Allen Brain Atlas data portal.<sup>xix</sup> Already, the BrainSpan Atlas has been used to identify genetic networks relevant to autism and schizophrenia.<sup>27,28</sup> In both of these studies, the fetal pattern of gene expression revealed relationships that could not be detected by studying gene expression in the adult brain. As most mental illnesses are neurodevelopmental, mapping where and when genes are expressed in the brain provides a fundamental atlas for charting risk.

“A comprehensive, high-resolution anatomic and molecular atlas of the developing brain is a first step to understanding what can go wrong. Many neuropsychiatric diseases are likely the result of abnormal brain development during prenatal life. Knowledge of where and when a particular gene is used may lead to future treatment targets and early interventions.”

Ed Lein, Ph.D.  
Allen Institute for Brain Science



The recently created BrainSpan Atlas of the Developing Human Brain incorporates gene activity or expression (left) along with anatomical reference atlases (right) and neuroimaging data (not shown) of the mid-gestational human brain. In this figure, the location and expression level of the gene *TGIF1* is shown in a brain from 21 weeks postconception.

Source: Allen Institute for Brain Science

<sup>xix</sup> To access the Allen Brain Atlas data portal, see: <http://www.brain-map.org/>.



STRATEGIC OBJECTIVE 3 lays out the next steps in the research continuum for identifying better preventive and therapeutic interventions, and for tailoring such interventions to the individual.

## Strategic Objective 3: Strive for Prevention and Cures

There is little doubt that we need better biomedical and psychosocial treatments for mental illnesses. A recent study<sup>29</sup> demonstrates how mental illnesses are a leading source of disability, with disability increasing since 1990 despite a concomitant rise in the use of pharmacologic treatments.<sup>30</sup> Although there are many commercially successful medications for anxiety, depression, and psychosis, they are largely variations of existing compounds; few represent true breakthroughs in efficacy.<sup>31</sup> For many serious clinical challenges, such as PTSD, the core symptoms of autism, the cognitive deficits of schizophrenia, and anorexia nervosa, to name a few, we lack effective medications altogether. There has been more success recently in the development of psychosocial interventions, with important progress in such challenging conditions as borderline personality disorder and anorexia nervosa. However, even the most effective psychotherapeutic interventions, like cognitive behavioral therapy for mood and anxiety disorders, do not work for everyone. A successful path to better treatments requires more precise diagnostics, validated targets, strategies for individualization, and mechanisms for scaling interventions for broad impact.

More precise diagnostics should emerge from the RDoC project. By reconceptualizing the scientific study of mental illnesses in an integrative and dimensional way, we are forging a path to a future where measures of an individual's genetic, neural, physiological, and behavioral states will form the basis of an increasingly specific and informative diagnosis. RDoC-based classifications should facilitate the identification and validation of biomarkers for subtypes of mental illness and for response to specific interventions. NIMH envisions such biomarkers as integral to a better system of care where care providers have the objective tools needed to diagnose, tailor treatment, and monitor response systematically. If successful, RDoC will not only deconstruct current categories like major depressive disorder into several subtypes requiring different treatments, it will also identify dimensions like anhedonia that span several current categories and might be addressed by new interventions.

For illnesses in other areas of medicine, increased understanding of their biological bases has transformed previously dire diagnoses into manageable, if chronic, illnesses. For example, we have seen dramatic improvements in remission rates for specific types of cancer and large drops in mortality rates from cardiovascular disease. We have not seen equivalent improvements for mental illnesses, which can be no less deadly or disabling. NIMH now requires that clinical trials identify the target

(e.g., a neural pathway or a cognitive domain) of the treatment being studied and measure the extent to which a given dose of the intervention affects the target. This approach uses interventions not only as potential treatments, but as tools to probe the mechanisms that may underlie an individual’s disorder. This target-focused strategy is designed to quickly identify those interventions that merit more extensive testing and to identify targets for additional candidate interventions. The promise of better treatments, whether pharmacological, psychosocial, device-based, or a combination of the three, depends on clinical trials that rapidly validate or, as importantly, reject specific mechanisms.

Intervention research has historically focused on the elimination or reduction of symptoms of mental illnesses. Alleviating symptoms, although vital, may not address the totality of a person’s quality of life. Therefore, NIMH will work toward person-centered approaches that take into consideration the individual’s precise diagnosis (using an RDoC approach), environmental and cultural factors, characteristics of the interventions (including their efficacy, tolerability, and availability), and the individual’s characteristics and preferences (including those captured in person-centered treatment plans).



We are in a dynamic period of change for mental health care. With new legislation affecting health care, new stakeholders, and new ways to conduct clinical research, the traditional intervention development “pipeline” is being transformed. NIMH will focus on intervention research with the greatest potential to transform practice and public health. NIMH envisions individuals receiving the most effective treatment at the earliest opportunity, with maximal impact on health outcomes and daily life. Treatment should be accessible across socioeconomic levels and among diverse groups (e.g., sex, gender, age, racial, ethnic, cultural), usable in diverse settings and with individuals with a range of illness severity and treatment responsiveness.

To further develop interventions that are based on precision medicine and are efficacious for the greatest number of people, NIMH will employ the following strategies:

### STRATEGY 3.1: DEVELOP NEW TREATMENTS BASED ON DISCOVERIES IN GENOMICS, NEUROSCIENCE, AND BEHAVIORAL SCIENCE

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While past pharmacological treatments have focused on monoamine transporters and neurotransmitter receptors, and psychotherapies have been based on traditional

learning theory, new discoveries are revealing a diverse range of potential targets for new interventions. The challenge is to test these potential mechanisms rapidly to rule in or rule out the target as a mechanism of the illness. This requires that the intervention engage the target and test its efficacy for reducing symptoms. New interventions are especially needed for those syndromes causing the greatest disability, and new measures are needed to assess reductions in disability. To implement this strategy, NIMH will support research to:

- Identify and validate new targets for treatment development that underlie disease mechanisms.
- Develop and validate new metrics for target engagement that are feasible for use in clinical trials.
- Develop objective surrogate measures of outcome and clinical change that extend beyond symptoms, to assess if target mechanisms underlying general health and quality of life have been modified by treatments.

## STRATEGY 3.2: DEVELOP WAYS TO TAILOR EXISTING AND NEW INTERVENTIONS TO OPTIMIZE OUTCOMES

Clinical trials in mental health have traditionally focused on individuals with diagnoses made on the basis of symptoms rather than stratifying individuals into subgroups based on behavioral or biological factors. As a result, clinical trials include highly heterogeneous groups and efficacy for a subgroup may be obscured. A relevant analogy here is to compare this situation with testing the efficacy of an antibiotic in everyone with a fever. Going forward, the quest for better treatments will depend on new diagnostics, such as RDoC domains, that identify subgroups with common etiologies or other features sensitive to treatment. To implement this strategy, NIMH will support research to:

- Develop valid and innovative biomarkers to detect subgroups of individuals sharing common etiologies—whether within or across traditional diagnostic categories—as well as aspects of emotion, cognition, and social behavior that predict clinical response.



- Foster personalized interventions and strategies for sequencing or combining existing and novel interventions that are optimal for specific phases of disease progression (e.g., prodromal, initial onset, chronic), different stages of development (e.g., early childhood, adolescence, adulthood, late life), and other individual characteristics.
- Develop and refine alternative research designs and analytic approaches that can be used to test precise interventions.

### STRATEGY 3.3: TEST INTERVENTIONS FOR EFFECTIVENESS IN COMMUNITY PRACTICE SETTINGS



NIMH strives to support intervention research that maximally improves the lives and functioning of people with mental illnesses. While most interventions are developed in academic settings, their value depends on translating successful outcomes to community practice settings. Moving from clinical research to clinical practice has been a challenge for both biomedical and psychosocial interventions. But this stage of translation can be accelerated by research, including research on the bundling of previously validated interventions to optimize their impact in community practice settings. This approach promises to move community practice beyond the single-pill or single-treatment approach.

This aspect of translation, sometimes called T2, can be leveraged by partnerships with other funders such as PCORI and the Clinical and Translational Science Awards program. Once such outcomes are optimized in pragmatic trials, they are ready for yet broader implementation in a variety of service settings and health care system models. To implement this strategy, NIMH will support research to:

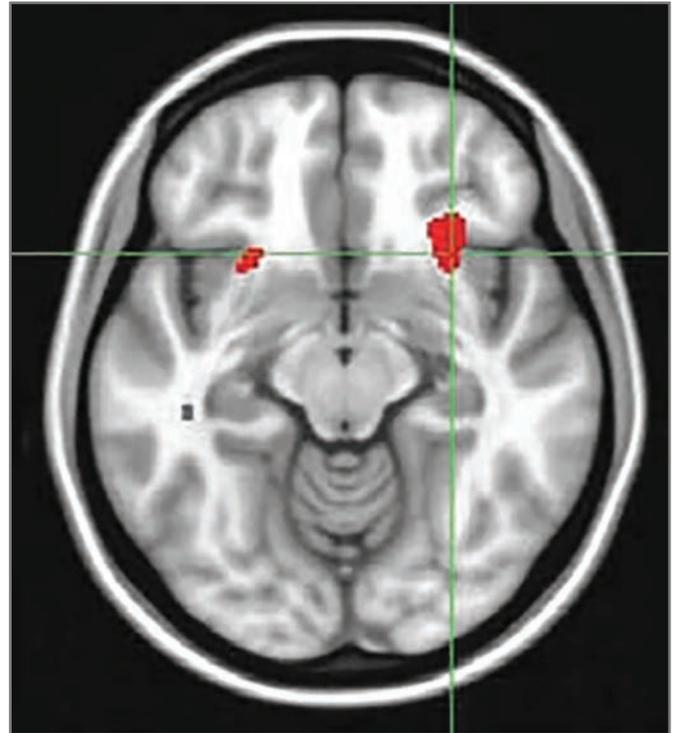
- Develop and test bundled intervention components (each validated individually in prior research) that have the greatest impact on patients' lives and functioning.
- Together with key stakeholders, including patient, provider, payer, and other research funding groups, conduct efficient pragmatic trials that employ new tools to rapidly identify, engage, assess, and follow participants in the context of routine care.
- Enhance the practical relevance of effectiveness research, taking into account how patient-, provider-, and organizational-level factors impact the outcomes of interventions in practice settings.

## Toward Signposts for Precision Medicine

Treatment selection in areas of medicine outside of mental health, such as cancer and heart disease, is increasingly based on an understanding of the multiple possible causes of these diseases in different individuals and the ability to use biomarkers<sup>32</sup> (e.g., indicators from blood and genetic tests) to guide and precisely tailor treatment. However, treatment of a condition like depression remains based largely on trial and error. A health care provider will try a treatment—a medication or psychotherapy—for a month or two to see if it works. As a result, fewer than 40 percent of patients achieve remission with their first treatment.<sup>33</sup> The time lost exacerbates an already lengthy delay before relief from the symptoms of depression can begin. And the financial impact of care is immediate, even though relief is not.

Because depression can emerge from many different underlying causes, it is unlikely that there will ever be a single treatment that works for everyone. Rather, what we can aim for is the ability to predict which particular treatment works for a particular individual. Early studies using positron emission tomography (PET) scans have provided information on the areas of the brain affected by depression and the effects of treatment. Recent studies showed that pretreatment scans of patients diagnosed with depression could predict which patients would respond to treatment with cognitive behavioral therapy (CBT) versus a standard antidepressant medication, escitalopram. Activity in one specific brain area—the insula—proved to be a reliable predictor of treatment outcome. Low resting brain activity in the front part of the insula indicated a higher likelihood of remission with CBT and a poor response to the antidepressant escitalopram. Conversely, high activity in the insula predicted remission with escitalopram and a poor response to CBT. This area of the insula is known to be important in regulating emotional states, self-awareness, decision making, and other cognitive tasks.

While PET scans are expensive and not likely to be used broadly, this research constitutes a proof of concept: the identification of biomarkers, such as distinctive patterns in a PET scan, can provide an evidence base for choosing the optimal treatment for each individual. The challenge is to find biomarkers (including cognitive performance) that are simple, inexpensive, and reliable predictors of treatment response.



*Low pretreatment resting brain activity in the front part of the insula (right side of the brain image—the red area where green lines converge) signaled a significantly higher likelihood of remission with CBT and a poor response to escitalopram. Conversely, hyperactivity in the insula predicted remission with escitalopram and a poor response to CBT. Image shows PET data superimposed on anatomic MRI scan data.<sup>33</sup>*

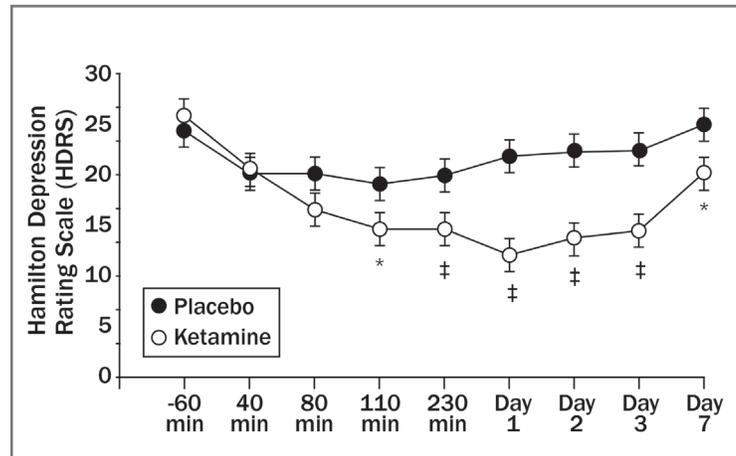
*Source: Helen Mayberg, M.D., Emory University*

# Ketamine: A New (and Faster) Path to Treating Depression

The most commonly used antidepressants are largely variations on a theme; they increase the supply within synapses of a class of neurotransmitters believed to play a role in depression. While these drugs relieve depression for some, there is a weeks-long delay before they take effect, and some people with “treatment-resistant” depression do not respond at all.

The delay in effectiveness has suggested to scientists that the medication-induced changes in neurotransmitters are several steps away from processes more central to the root cause of depression. One possibility for a more proximal mechanism is glutamate, the primary excitatory, or activating, neurotransmitter in the brain. Preliminary studies suggested that inhibitors of glutamate could have antidepressant-like effects, and in a seminal clinical trial, the drug ketamine—which dampens glutamate signaling—lifted depression in as little as 2 hours in people with treatment-resistant depression.<sup>34</sup>

The discovery of rapidly acting antidepressants has transformed our expectations—we now look for treatments that will work in 6 hours rather than 6 weeks. But ketamine has some disadvantages; it has to be administered intravenously, the effects are transient, and it has side effects that require careful monitoring. However, results from clinical studies have confirmed the potential of the glutamate pathway as a target for the development of new antidepressants. Continuing research with ketamine has provided information on biomarkers that could be used to predict who will respond to treatment.<sup>35</sup> Clinical studies are also testing analogs of ketamine in an effort to develop glutamate inhibitors without ketamine’s side effects that can then be used in the clinic.<sup>36</sup> Ketamine may also have potential for treating other mental illnesses; for example, a preliminary clinical trial reported that ketamine reduced the severity of symptoms in patients with PTSD.<sup>37</sup> Investigation of the role of glutamate signaling in other illnesses may provide the impetus to develop novel therapies based on this pathway.

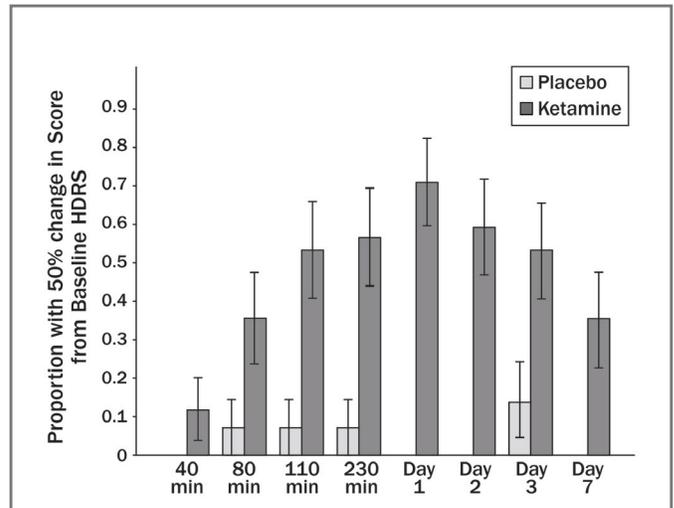


Change in the 21-item Hamilton Depression Rating Scale (HDRS) following ketamine or placebo treatment.<sup>34</sup>

Source: Carlos Zarate, M.D., Experimental Therapeutics and Pathophysiology Branch, NIMH

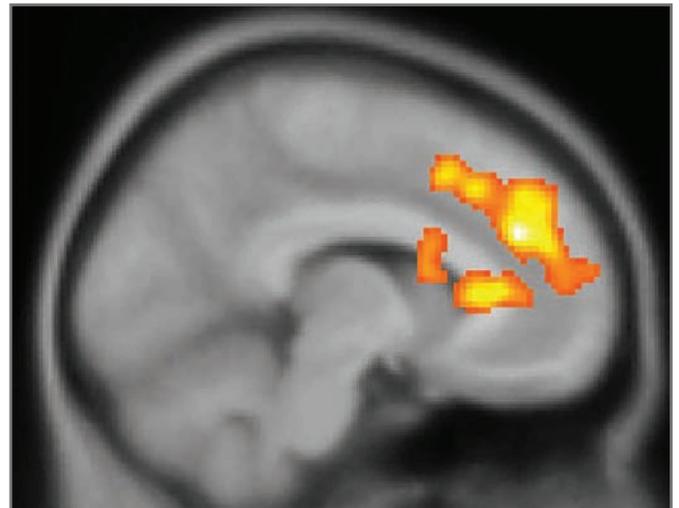
One of the imperatives of clinical research going forward will be to demonstrate whether the ability of a compound to interact with a specific brain target is related to some measurable change in brain or behavioral activity that, in turn, can be associated with relief of symptoms. In a study of ketamine's effects in patients in the depressive phase of bipolar disorder, ketamine restored pleasure-seeking behavior independent from and ahead of its other antidepressant effects. Within 40 minutes after a single infusion of ketamine, treatment-resistant depressed bipolar disorder patients experienced a reversal of a key symptom—loss of interest in pleasurable activities—which lasted up to 14 days.<sup>38</sup> Brain scans traced the agent's action to boosted activity in areas at the front and deep in the right hemisphere of the brain. This approach is consistent with the NIMH's RDoC project, which calls for the study of functions—such as the ability to seek out and experience rewards—and their related brain systems that may identify subgroups of patients with common underlying dysfunctions that cut across traditional diagnostic categories.

The ketamine story shows that in some instances, a strong and repeatable clinical outcome stemming from a hypothesis about a specific molecular target (e.g., a glutamate receptor) can open up new arenas for basic research to explain the mechanisms of treatment response; basic studies can, in turn, provide data leading to improved treatments directed at that mechanism. A continuing focus on specific mechanisms will not only provide information on the potential of test compounds as depression medications, but will also help us understand which targets in the brain are worth aiming at in the quest for new therapies.



Proportion of responders showing a 50 percent improvement on the HDRS following ketamine or placebo treatment.<sup>34</sup>

Source: Carlos Zarate, M.D., Experimental Therapeutics and Pathophysiology Branch, NIMH



PET scans revealed that ketamine rapidly restored bipolar depressed patients' ability to anticipate pleasurable experiences by boosting activity in the dorsal anterior cingulate cortex (yellow) and related circuitry. Picture shows PET scan data superimposed on anatomical MRI.<sup>38</sup>

Source: Carlos Zarate, M.D., Experimental Therapeutics and Pathophysiology Branch, NIMH



STRATEGIC OBJECTIVE 4 strives to bring the knowledge and findings derived from the previous Strategic Objectives to practice, to improve the reach and quality of existing services, and to develop novel evidence-based services.

## Strategic Objective 4: Strengthen the Public Health Impact of NIMH-Supported Research

The previous objectives focused on the development of new diagnostics and new therapeutics that will transform mental health care in the future. Unfortunately, the pace of discovery science is not a good match for the urgency of the public health need. The increasing prevalence of autism, the persistently high rates of suicide, the mental health needs of service members and veterans, the treatment delays experienced by youth with early psychosis, and the chronic disability and early mortality of serious mental illnesses are among the problems that demand a rapid response. Fortunately, we need not wait for the distant future to see research impact public health. A lesson from the NIMH Recovery After an Initial Schizophrenia Episode (RAISE) project is that services research can speed implementation of evidence-based care for early psychosis in community settings by optimizing the organization and delivery of current treatments. In the new mental health care landscape, there should be many opportunities to improve outcomes with new financing and care delivery models, with services provided outside the traditional health care systems (in schools, in community settings, at workplaces, and online), and with care integration. NIMH's role is to support the science that capitalizes on these opportunities, providing the best evidence about how to organize care to ensure the best outcomes.

How can NIMH strengthen the public health impact of its research? One approach involves partnering with payers (e.g., Medicaid, commercial insurers), regulators (e.g., U.S. Food and Drug Administration), and local, state, and Federal decision makers to determine what research will provide the requisite evidence for improving outcomes in the world of practice. A second approach develops new modes of health care service delivery, for example, the expansion of developmentally focused team-based care as in the RAISE project. A third approach, based on the learning health care system concept, builds a feedback loop between practice and research so that each encounter with a person receiving care yields data that are used to improve the care system on an ongoing basis.



The next 10 years will see more change in the mental health ecosystem that will affect how we provide care. Technological advances such as real-time availability of health information, remote sensing of health status over time, and a fundamental shift in how individuals interact with the health care system and providers (e.g., email, texting, online social networks) have the potential to improve an individual's care experience. Yet strategic questions must be answered for technology's promise to materialize. What are the critical targets for improving the care delivery system and improving mental health outcomes in diverse populations (e.g., sex, gender, age, race, ethnicity)? How can research contribute to creating and using new tools to address those targets? In what new ways can health care data be leveraged to address pressing patient, provider, and system-level needs? Which research methods are best suited for assessing public health impact? These complex questions demand us to ask: what partnerships must exist to address these questions efficiently and effectively? For stakeholders, a learning mental health care (LMHC) system provides the necessary forum for collaboration and shared responsibility. For those receiving care, LMHC means that care decisions are more frequently based on data, the practice of care will be subject to ongoing improvements based on broader arrays of information, and lessons learned will be shared across providers and patient networks. In LMHC, the consumers of care are at the center and are engaged as full partners in the process. To improve evidence-based services that reach the broadest population, NIMH will employ the following strategies:

## STRATEGY 4.1: IMPROVE THE EFFICIENCY AND EFFECTIVENESS OF EXISTING MENTAL HEALTH SERVICES THROUGH RESEARCH



Right now, research can reveal opportunities to improve care. At all levels, and across sectors, leverage points exist to optimize the current standard of care. Local innovations have the promise to improve system outcomes, but are understudied and thus lack an evidence base that is sufficient to promote scale-up. In other situations, existing mental health services have limited effectiveness and need target-based approaches to improve delivery of high-quality and efficient care. Particularly within the area of serious mental illnesses, we need research on the impact of alternative strategies to provide and pay for care in public and private health systems (e.g., accountable care organizations, bundled payment mechanisms,

performance-based financing). To implement this strategy, NIMH will support research to:

- Employ existing real-world data collection systems to identify strategies for improving access, quality, and equity of mental health services in diverse populations.
- Identify, validate, and scale up innovative programs currently in use that improve mental health services for underserved populations.
- Optimize financing models for adults and children with serious mental illnesses to provide efficient and effective care in public and private health care systems.

## STRATEGY 4.2: ESTABLISH RESEARCH-PRACTICE PARTNERSHIPS TO IMPROVE DISSEMINATION, IMPLEMENTATION, AND CONTINUOUS IMPROVEMENT OF EVIDENCE-BASED MENTAL HEALTH SERVICES

The delay between research and practice is too long, and limitations in uptake of effective mental health interventions are widespread. We need large-scale change that broadly improves public health. Research to improve the dissemination, adoption, implementation, and sustainability of evidence-based interventions can reduce the lag between research discovery and clinical practice, radically alter the quality of care provided for people, and reduce disparities in access and quality of care for underserved and diverse populations. Dissemination and implementation research requires expanded partnerships with stakeholders who oversee the provision and financing of care, as well as those who directly benefit from evidence-based approaches (e.g., service users and caregivers). By necessity, these partnerships must leverage complementary efforts of other Federal agencies (e.g., SAMHSA, Centers for Medicare & Medicaid Services) and institutions with common interests and activities (e.g., PCORI, state agencies, private and public health care systems). To effect this strategy, NIMH will support research to:

- In partnership with key stakeholders, develop and validate strategies for implementing, sustaining, and continuously improving evidence-based practices.
- Build models to scale up effective interventions for use in public and private primary care, specialty care, and other systems.
- Develop decision support tools that increase the effectiveness and continuous improvement of mental health interventions in public and private primary care, specialty care, and other systems.

## STRATEGY 4.3: DEVELOP INNOVATIVE SERVICE DELIVERY MODELS TO IMPROVE DRAMATICALLY THE OUTCOMES OF MENTAL HEALTH SERVICES RECEIVED IN DIVERSE COMMUNITIES AND POPULATIONS



Evidence suggests that current service delivery models are inadequately organized to meet the needs of the U.S. population. New models of service delivery that move beyond traditional care systems and address challenges posed by an insufficient workforce and limited capacity for monitoring and following up care (e.g., drawing from lessons learned in global mental health research conducted in low- and middle-income countries) could significantly improve the impact of mental health services on population health. We must circumvent the traditional shortcomings of mental health care by developing and testing novel components of care across multiple settings where mental health services are needed, and use advanced tools to better reach the population and deliver immediate, appropriate, and progressively improving care. To implement this strategy, NIMH will support collaborative research to:

- Develop systems-level strategies in nontraditional mental health care settings using technology and other approaches to identify, support, and monitor the effectiveness of care for individuals with mental illnesses.
- Develop and validate service delivery models that provide responsive and preemptive evidence-based supports for individuals throughout the course of illness.
- Develop and validate coordinated medical decision-making models that bridge multiple social and medical care settings to integrate the appropriate care for people with serious mental illnesses and multiple chronic conditions.

## STRATEGY 4.4: DEVELOP NEW CAPACITY FOR RESEARCH THAT EVALUATES THE PUBLIC HEALTH IMPACT OF MENTAL HEALTH SERVICES INNOVATIONS

Tools available to improve mental health services have shifted rapidly toward approaches that emphasize team-based care, systems integration, technological developments, data aggregation, and new financing models. The next generation of investigations will require a range of platforms to study the prevalence of mental illnesses, quality of care, practice variations, and the impact of new innovations on access, efficiency, clinical outcomes, and epidemiologic indicators. New research designs, measures, and statistical approaches will be needed to support rapid testing of system improvement efforts and to facilitate analysis of complex data arising from the growing digital enterprise. To achieve high-impact public health research, new training models will be required that embrace new opportunities, including advanced information and communication technologies, and assessment and analytic strategies for complex data. Finally, we need to harness new opportunities afforded by citizen-centered science and crowdsourcing. These approaches provide collective expertise and evidence to help shape research questions and optimally answer them. To implement this strategy, NIMH will support research to:

- Develop assessment platforms within service systems that allow ongoing monitoring of mental illness prevalence, service access, quality, efficiency of care, and outcomes in diverse populations and settings.
- Develop valid and reliable measures of treatment quality and outcomes that can be feasibly applied at the person, clinic, system, and population levels.

# Learning Mental Health System—Narrowing the Gap from Science to Service

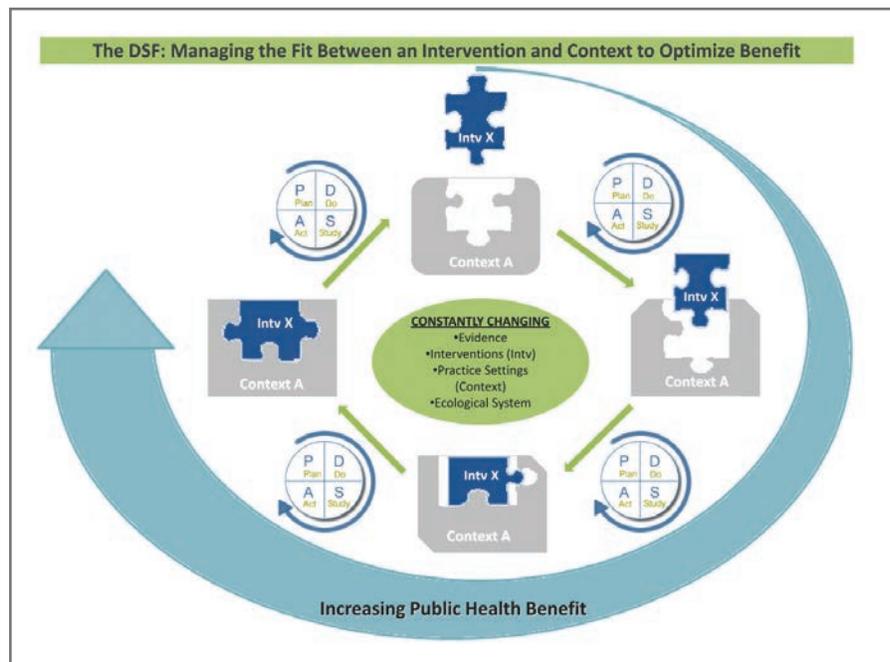
The mental health care system can learn a thing or two from business. Nearly every business collects metrics on inventory, sales, and workplace process. In contrast, mental health care has been slow to measure these kinds of outcomes, taking more than a decade to incorporate research results into community care programs. Increasingly, mental health care, via either managed care or large practice settings, is improving by collecting data through electronic health records and refining practice based on what works—becoming, in essence, a “learning mental health system” (LMHS).<sup>39</sup>

Looking to narrow the time gap for feedback to guide practice, the Seattle-based Mental Health Research Network (MHRN) has integrated electronic health records for 12.5 million patients with mental illnesses across 13 health system research centers. Now, the MHRN is better equipped to answer questions about suicide prevention and management of depression.<sup>xx</sup> Similarly, the Boston-based Mood Patient Powered Research Network is creating a cohort of 50,000 people with major depressive disorder or bipolar disorder to serve as a platform for mood disorder research. Results from both groups will aid in identifying best practices, tracking outcomes, and improving mental health care.<sup>xxi</sup>

Programs like these are providing models for how the health care community can ensure that the lessons learned from research and clinical experience are systematically and rapidly put to use to improve patient care.

<sup>xx</sup> For more information, see the Mental Health Research Network website: <http://www.mhresearchnetwork.org>.

<sup>xxi</sup> For more information, see the National Patient-Centered Clinical Research Network website: <http://pcomet.org/patient-powered-research-networks/ppm9-massachusetts-general-hospital/>.



The Dynamic Sustainability Framework (DSF) depicts a dynamic view of sustainability, which allows for the evolution of an intervention within a changing delivery system.<sup>40</sup> The changes in the shape of the puzzle pieces and of the contexts reflects the ongoing change to interventions, practice settings, and care systems, and shows the use of quality improvement methods to optimize the “fit” and improve the public health benefit of sustained use of interventions.

Source: David Chambers, D. Phil., Services Research and Clinical Epidemiology Branch, Division of Services and Intervention Research, NIMH

# A Therapist in One's Pocket: mHealth to Improve Access to Mental Health Care

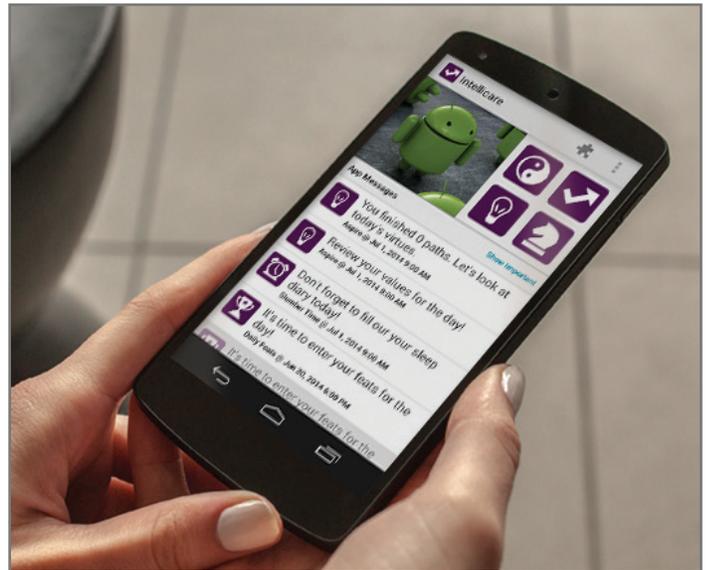
Less than half of individuals struggling with a mental illness receive services. The reasons for this disparity between need and service uptake include the cost of medication or therapy, regional scarcity of mental health professionals, inability to access mental health services due to distance and time, and, in some cases, resistance to seeing a mental health professional. So-called behavioral intervention technologies, or BITs—such as smartphones, wearable sensors, and video games—have the capacity to change this situation.

Many of the devices used by people every day—smartphones, tablets, and laptops—have sensors built in that are constantly capturing data on location, movement, and communication. We are beginning to explore the use of these devices to create real-time pictures of emotional state. How can technologies

be further harnessed to address mental health care needs? We currently use mobile technologies for improving adherence to treatment or for collecting passive data about activity or sleep, but the additional possibilities of these technologies are just emerging.

Approaches on the cutting edge of mental health mobile technologies use patient-initiated dialogue (think Siri as a psychotherapist) or personalized messages keyed to environmental cues—such as proximity to an anxiety-inducing stimulus detected by a GPS system.<sup>41</sup> Social prosthetics for autism are being developed for detecting facial expressions and translating them into words describing emotions. Other potential therapeutic opportunities include the use of social media and gaming to develop group support and increase resilience via cognitive training games.

Reports that online cognitive behavioral treatment can be as effective as in-person psychotherapy suggest that technology will expand access, extend the therapist impact, and expedite treatment.<sup>42</sup> For those with the most disabling illnesses, these tools will extend rather than replace the therapist. A recent report noted that over 40,000 new mobile health applications are available for download.<sup>43</sup> The promise of technology for improving diagnosis and treatment—and the need to establish an evidence base for efficacy—demands the attention of the research and technology communities, and NIMH.



*Intellicare, a smartphone app to serve users with anxiety or depression, holds promise for improving access to mental health care.*

*Source: David Mohr, Ph.D., Northwestern University*

## APPENDIX: DEVELOPMENT AND COMMENT PROCESS FOR THE NIMH STRATEGIC PLAN FOR RESEARCH

This NIMH Strategic Plan for Research is an update of the 2008 NIMH Strategic Plan, retaining core elements of the earlier Plan and revising as well as adding sections in response to the many changes in the field over the past 6 years.

We began with updating the Institute's overarching Strategic Objectives; this included identifying knowledge gaps and opportunities for research advancement. The four Objectives are broad goals that capture the diversity of topics the Institute must focus on to achieve its mission. The Objectives successively build in scale from basic neuroscience and behavioral science to research on mental health services. These four Strategic Objectives are:

- 1. Define the mechanisms of complex behaviors.**
- 2. Chart mental illness trajectories to determine when, where, and how to intervene.**
- 3. Strive for prevention and cures.**
- 4. Strengthen the public health impact of NIMH-supported research.**

We know that the specifics in this Plan may soon be obsolete as science has a way of taking us to places we could never predict. But the process of developing a plan with a diverse community of stakeholders has been valuable and will, we hope, be sustained by a shared commitment to progress even when the specific aims or strategies shift in response to the latest discoveries. Woodrow Wilson famously said, "I not only use all the brains I have, but all I can borrow." In that spirit, this final Plan was the product of many authors.

An early draft Plan was reviewed by the National Advisory Mental Health Council, which made several substantive suggestions. A revised draft was reviewed and discussed by the NIMH Alliance for Research Progress, a gathering of the major foundations and mental health research advocacy groups. To reach out to the scientific community and professional societies as well as the general public, a further revised draft Plan was published for public comment (comments could be submitted via email or postal address) through an announcement on the NIMH website and a Federal Register Notice from November 12, 2014, to December 11, 2014. In total, the Institute received nearly 600 comments from individuals, groups, and organizations. After numerous edits to address these comments, the penultimate draft was reviewed and discussed by the National Advisory Mental Health Council before finalizing the Plan.

We would like to thank everyone who took the time to review and provide feedback on the draft NIMH Strategic Plan for Research. We look forward to your continued involvement as we strive toward research that will result in the NIMH goals of prevention, recovery, and cure.

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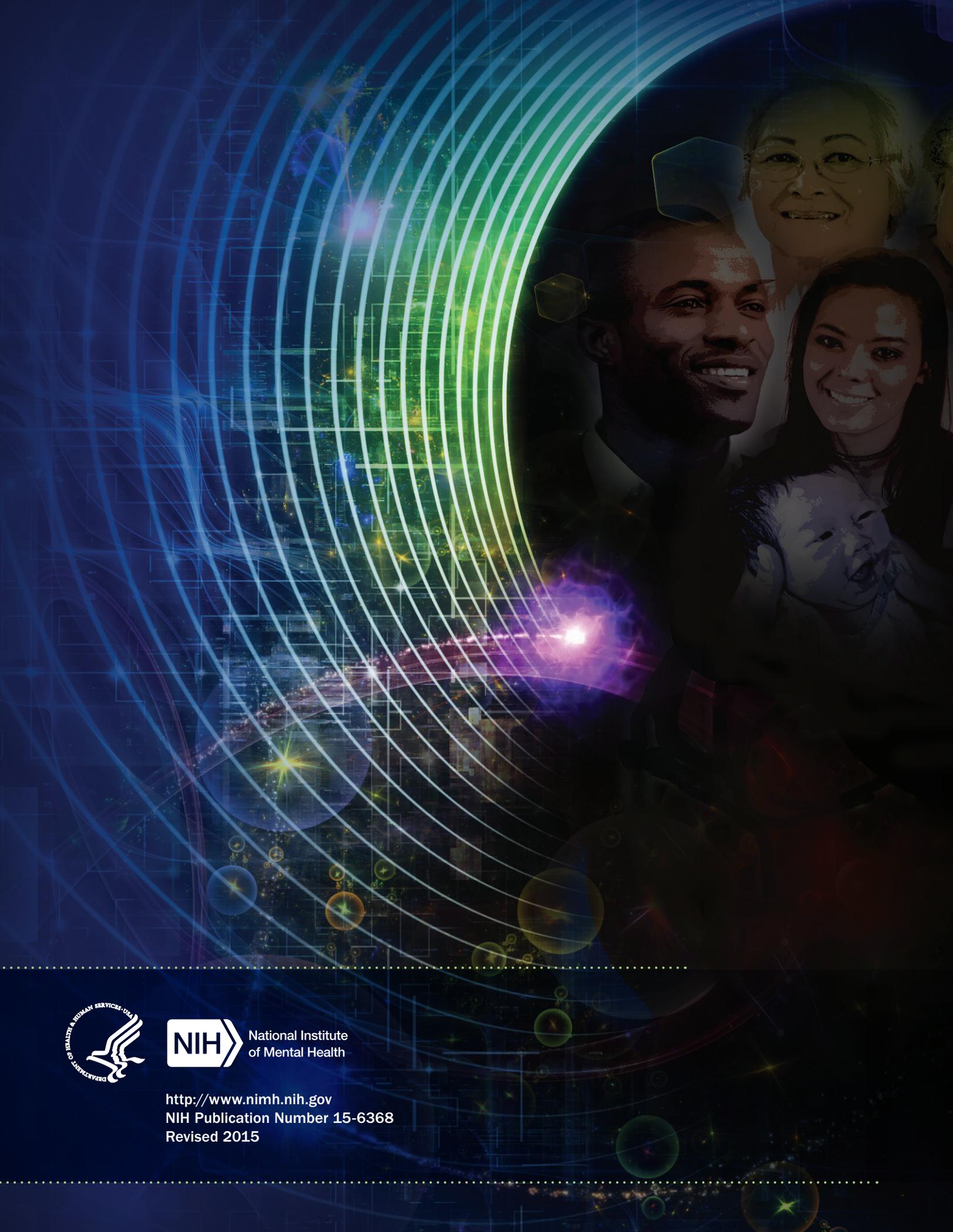
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