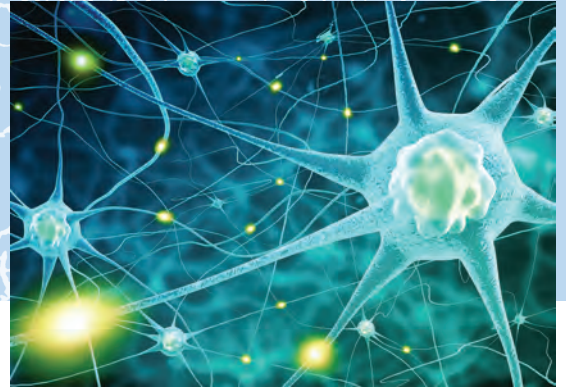
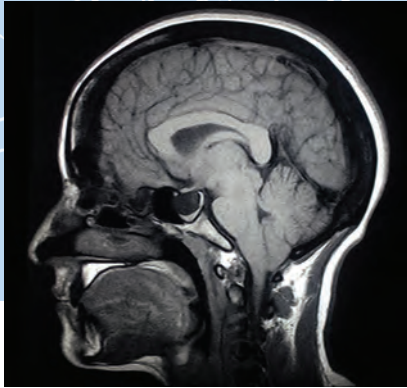


The National Academies of
SCIENCES • ENGINEERING • MEDICINE



Forum on Neuroscience and Nervous System Disorders

2016 Annual Report

Message from the Chairs

Steven Hyman and Story Landis

Nervous system disorders are common, major causes of premature mortality, and, in aggregate, the largest cause of disability worldwide. The public health and economic burden of these disorders do not capture the extraordinary distress to individuals and families caused by conditions such as depression, schizophrenia, Alzheimer's disease, chronic pain, amyotrophic lateral sclerosis (ALS), or addiction. Given the complexity and inaccessibility of the living human brain, there remain important gaps in our understanding of underlying disease mechanisms and, therefore, a lack of biomarkers to track disease progression and assess the effect of interventions, and a dearth of potential molecular targets for new therapies. In addition, many brain disorders cannot be modeled effectively in animals, impeding traditional paths toward target validation used by industry. Such scientific challenges, together with the lengthy clinical trials required to study treatments for neurodegenerative disorders and many other brain disorders, continue to stall development of both small and large molecular therapeutics. Better understanding of disease mechanisms would also facilitate new approaches to nervous system therapeutics strategies such as gene therapies, genome engineering, various forms of neuromodulation, and brain–computer interfaces. While these advances offer promise, they also raise important ethical, legal, and societal issues that have become a major focus of attention among diverse stakeholders including government, foundations, and academia.

The National Academies of Sciences, Engineering, and Medicine's Forum on Neuroscience and Nervous System Disorders provides an important venue for candid discussions about emerging and critical issues among key stakeholders, including federal agencies that serve as research sponsors and regulators; the private sector; the academic community; and the nonprofit sector, including foundations and groups focused on nervous system disorders. Through the Forum's activities, participants have been better able to share information and concerns and to understand each other's goals and priorities. The dialogue has often yielded ideas for concrete actions or produced new collaborations.

In 2016, discussions in membership meetings and large public workshops addressed a wide range of topics including opportunities to improve the integrity and efficiency of neuroscience clinical trials through enhanced design approaches; venture capital priority setting for areas within neuroscience ready for commercialization; the development, application, and regulation of multimodal therapies (e.g., behavioral, pharmaceutical, and device combinations) for nervous system disorders; international drug repurposing initiatives for brain disorders; and the development of clinical interventions in the absence of predictive animal models of human disease. In collaboration with the Organisation for Economic Co-operation and Development and other international stakeholders, the Forum also held a session that used non-invasive neuromodulation as a case study to discuss how ethical, legal, and social issues and responsible research innovation are integrated throughout research, development, and regulation of novel neurotechnologies.

Looking ahead to 2017, the Forum plans to address important topics including biomarker identification and development in neuroinflammation, a process implicated in a wide range of neurological and psychiatric disorders; barriers and opportunities in therapeutic delivery to the central nervous system by improving methods for traversing the blood–brain barrier; and the development of pharmaceutical strategies to address the opioid crisis.

We look forward to another productive year for the Forum.



Steven Hyman
Chair



Story Landis
Vice-Chair

Reflecting Back

Forum Activities in 2016

Neuroscience Trials of the Future

Although major strides have been made over the past two decades in basic neurosciences, the translation of new discoveries into more effective treatments has proven slow and difficult. Among the many factors impeding advances in therapeutics is stasis in clinical trials methodology, notwithstanding improvements in electronic data acquisition and analysis. Better methods—from clinical study design through execution and evaluation—could help enhance the feasibility, efficiency, and economic viability of clinical therapeutics development for brain disorders. The Forum convened a public workshop bringing together key stakeholders to discuss opportunities to improve the design and conduct of clinical trials for nervous system disorders (focusing specifically on Phase II and Phase III trials). Workshop participants considered strategies to advance therapeutic development for nervous system disorders, such as using innovative clinical trial designs; improving patient selection, engagement, and retention; and enhancing clinical monitoring to help decrease the failure rate of drugs and devices in development.

Multimodal Therapies for Brain Disorders

Numerous studies have shown that combining therapies of different modalities (e.g., drugs, devices, psychosocial interventions) may be more efficacious than monotherapy for many diseases and disorders. This model, however, has not been used for many brain disorders. The Forum hosted a public workshop to examine scientific, clinical, regulatory, and reimbursement issues related to multimodal approaches and identify potential opportunities to enhance clinical outcomes for individuals with psychiatric and neurological disorders. The workshop aimed to examine general principles, barriers, and potential solutions and opportunities that may apply across multimodal therapy development for brain disorders. Given the complexity of multimodal therapies, several workshop participants discussed the importance of directed research funding and collaborations in the precompetitive space to tackle preclinical issues, such



as biomarker identification and validation. Workshop participants also considered clinical trial designs (e.g., adaptive and platform trials) that might better quantify the additive or synergistic effects of multiple treatments.

Therapeutic Development in the Absence of Predictive Animal Models of Nervous System Disorders

Although the prevalence and burden of nervous system disorders remains high, development of new therapeutics lags behind other disease areas. Gaps in understanding of the underlying mechanisms of disease, a dearth of biomarkers, and limitations in the use of animal models to predict drug efficacy for human brain disorders have contributed to a high rate of late stage failures in drug development. As a result, many large pharmaceutical companies have decreased investment in or withdrawn entirely from their neuroscience research programs. Building on previous Forum workshops (Improving Translation of Animal Models for Nervous System Disorders [2012] and Accelerating Therapeutic Development for Nervous System Disorders Toward First-in-Human Trials [2013]), the Forum

convened a public workshop to examine the evidence needed to bring compounds that appear to be safe into human efficacy trials in the absence of a predictive animal model, including ethical, regulatory, pragmatic, and financial considerations. The workshop brought together key stakeholders to discuss scientific, regulatory, and business challenges and to identify potential opportunities in this domain to motivate and accelerate therapeutic development to address unmet medical needs. Workshop participants discussed several innovative modeling paradigms for nervous system disorders, such as computational modeling of brain circuits using quantitative systems pharmacology, modeling disease in human induced pluripotent stem cells, and using gene editing techniques in nonhuman primates to create models that more closely resemble humans. In addition, several workshop participants noted the importance of using human clinical trial data to further the field's understanding of disease mechanisms and opined closer collaborations between clinicians and researchers.

Neurotechnology and Society: Strengthening Responsible Innovation in Brain Science

Emerging neurotechnologies have the potential to enhance human lives by offering better health outcomes and higher quality of life through the prevention and treatment of mental illness and neurological disease. However, these new technologies raise a host of ethical, legal, and social issues. Large-scale brain initiatives are deepening our understanding of how a healthy brain functions and developing new tools to address open questions in fundamental neuroscience. These new tools in turn permit the elucidation of the biological underpinnings of neuropsychiatric diseases. With these efforts will come the potential to manipulate brain function both in illness and in health. There is broad international agreement that ethical considerations should be integrated into the research under way and emerging from the brain initiatives. Although the National Institutes of Health and other federal agencies have begun to

consider research programs on ethical, legal, and social issues, to date there have been only limited opportunities to compare approaches across the different national and regional initiatives, jurisdictions, and technologies. The Organisation for Economic Co-Operation and Development—with collaboration from the Forum and other organizations internationally—convened a meeting to share ideas for understanding and addressing the societal implications of new neurotechnologies. Building on the Forum’s 2015 workshop, Non-Invasive Neuromodulation of the Central Nervous System, the public session organized by the Forum used non-invasive neuromodulation as an example to explore how ethical, legal, and social issues and responsible research and innovation are integrated into research, development, and regulation in different countries. Given the low adoption rate of non-invasive neuromodulation in clinical settings, session participants discussed the importance of aligning regulatory requirements with reimbursement decisions, educating providers and the public on the potential benefits and harms of these technologies, and developing professional guidelines informing clinical and over-the-counter uses.

Looking Forward

Forum Activities in 2017

Biomarkers of Neuroinflammation

Innate and adaptive immunity have become very important areas of investigation for psychiatric disorders, neurologic disorders, neurodevelopmental disorders, and neurodegeneration resulting from traumatic brain injury. For example, genetic and other biologic data are demonstrating critical roles of innate and adaptive immunity in Alzheimer's disease pathogenesis. Several conferences and meetings are being held in this exciting area, but it is not clear how best to translate recent findings to therapeutics—developing biomarkers that can be validated and used in clinical development and regulatory decision making is a critical step in this process. Many efforts are already under way to identify biomarkers of neuroinflammation, including biomarkers in cerebrospinal fluid and blood, as well as PET (positron emission tomography) imaging agents for targets such as TSPO (translocator protein). Given the intense activity in academic-research and private-sector settings and across many nervous system disorders, there is an opportunity to take stock of current knowledge, provide a venue for coordination, and identify potential opportunities to advance work in this domain. This public workshop will bring together key stakeholders from government, academia, industry, and disease-focused organizations to explore and advance efforts to identify biomarkers of neuroinflammation that can be validated and used in clinical development and regulatory decision making.



Enabling Novel Treatments for Nervous System Disorders by Improving Methods for Traversing the Blood–Brain Barrier

The blood–brain barrier (BBB) presents a special challenge to the development of therapeutics for many central nervous system (CNS) disorders. Far from acting simply as a physical barrier, the BBB is a complex dynamic system involving several cell types, passive and active transport mechanisms, and adaptive function to control the exchange of substances between blood and CNS fluids. Few substances readily traverse the BBB to reach the brain or spinal cord, including most small molecules and the vast majority of large molecules such as proteins like antibodies, growth factors, oligonucleotides, and viral vectors. However, there are now emerging clinical data suggesting that certain monoclonal antibodies may have disease-modifying effects in various neurodegenerative and neuroinflammatory disorders, such as Alzheimer’s disease and multiple sclerosis. Improved methods for increasing the levels of these antibodies and many other therapeutic proteins in the brain—by getting more across the BBB—may enhance their therapeutic benefits. The Forum will convene a workshop to discuss the current state of the science and explore challenges and opportunities for improving methods for traversing the BBB and, in particular, for delivering large molecules, such as monoclonal antibodies, small interfering ribonucleic acids, and recombinant proteins, to target areas in the CNS.

Opportunities and Challenges to Developing Non-Opioid Alternatives for Treating Pain

Pain is a leading cause of disability in the United States, affecting more people than cancer, diabetes, and heart disease combined (American Academy of Pain Management, 2016; NIH, 2016). Many physicians have come to prescribe opioids to their pain patients, and pain patients have come to expect such prescriptions. The resulting dramatic increase in opioid prescriptions within the last decade has been a major factor contributing to the opioid epidemic the country currently faces, with alarming rates of misuse, abuse, and overdose deaths. In 2017, the National Institutes of Health will host three small meetings focused on creating public-private partnerships to address the urgent public health need associated with opioids. Specifically, the meetings will bring together pharmaceutical industry leaders to explore the formulation of opioid drugs, develop additional drugs to treat opioid overdoses, and create non-opioid alternatives for pain. The Forum will host a public workshop that brings together key stakeholders to build on the discussions from the NIH meetings and to examine potential implementation challenges and opportunities to address them.

Working Groups

The Forum has working groups to provide additional opportunities to address selected topics. Workshop topics may emerge from these efforts; any such workshops are then organized by an independently appointed workshop planning committee.

Clinical Research Data Sharing

The Forum is participating in an activity on clinical research data sharing that is a collaboration of four National Academies forums (focusing on neuroscience; drug discovery, development, and translation; genomics; and cancer). Building on the National Academies Consensus Study Report *Sharing Clinical Trial Data: Maximizing Benefits, Minimizing Risk* (2015), the group's goals are:

- **Coordination.** Through communication and organization, improve coordination and collaboration among stakeholders engaged in activities related to data sharing. Contribute to a learning system where stakeholders share information on the outcomes of projects and policies. Provide support and a venue to foster the potential development of a multi-stakeholder body to discuss clinical trial data sharing.
- **Implementation.** Support implementation efforts by creating a mechanism for collaborative participants to identify priority issues, and convene or organize other activities where appropriate. Priorities and action items are determined by action collaborative participants and executed by them, with National Academies staff support, in their individual and organizational capacities.

Training a Neuroscience Workforce

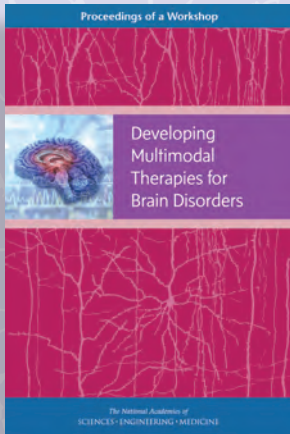
Building on discussions from the 2014 Forum workshop Defining the Expertise Needed for the 21st Century Neuroscience Workforce, the Forum established a working group to continue to examine the current challenges and gaps in neuroscience training and identify opportunities to strengthen training programs so that they are tailored to meet the current and future workforce needs. In 2016, members of the working group continued to foster discussions in this area through their participation on scientific panels and in online discussions and by authoring a Perspective in *Neuron* titled "Neuroscience Training for the 21st Century."



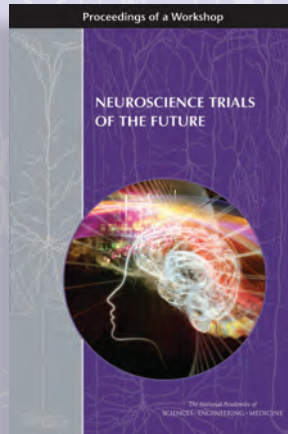
Mental, Neurological, and Substance Use Disorders in Sub-Saharan Africa

The Forum has a longstanding interest in identifying innovative solutions to enhance care for mental, neurological, and substance use disorders in sub-Saharan Africa. Since 2009, the Forum has hosted five workshops in Ethiopia, Ghana, Kenya, and Uganda to examine both general and country-specific barriers and potential innovative solutions, with particular focus on increasing human and financial resources to support current and future efforts. Using tools set forth by the World Health Organization, the Forum, in collaboration with global entities, is continuing to explore additional opportunities to contribute in this area.

2016 Publications



**Developing Multimodal Therapies
for Brain Disorders: Proceedings of a
Workshop**



**Neuroscience Trials of the Future:
Proceedings of a Workshop**



2016 Forum publications have been downloaded in more than
123 countries, for a total of more than **5,300 times**.

Forum Members

(as of December 2016)

Steven Hyman (Chair)

Broad Institute of the Massachusetts
Institute of Technology and Harvard
University

Story Landis (Vice-Chair)

Former Director, National Institute of
Neurological Disorders and Stroke

Susan Amara

Society for Neuroscience

Rita Balice-Gordon

Sanofi

Katja Brose

Cell Press

Emery Brown

Harvard Medical School and the
Massachusetts Institute of Technology

Daniel Burch

Pharmaceutical Product Development,
LLC

Joseph Buxbaum

Icahn School of Medicine at Mount
Sinai

Sarah Caddick

Gatsby Charitable Foundation

Rosa Canet-Aviles

Foundation for the National Institutes
of Health

Maria Carrillo

Alzheimer's Association

E. Antonio Chiocca

Harvard Medical School

Timothy Coetzee

National Multiple Sclerosis Society

Jonathan Cohen

Princeton University

Fay Lomax Cook

National Science Foundation

William Dunn

Food and Drug Administration

Joshua Gordon

National Institute of Mental Health

Hank Greely

Stanford University

Raquel Gur

University of Pennsylvania Medical
Center

Magali Haas

Cohen Veterans Bioscience

Ramona Hicks

One Mind

Richard Hodes

National Institute on Aging

Stuart Hoffman

Department of Veterans Affairs

Michael Irizarry

Eli Lilly and Company

Inez Jabalpurwala

Brain Canada Foundation

Frances Jensen

University of Pennsylvania Health
System

George Koob

National Institute on Alcohol Abuse
and Alcoholism

Walter Koroshetz

National Institute of Neurological
Disorders and Stroke

Alan Leshner

Chief Executive Officer Emeritus,
American Association for the
Advancement of Science

Husseini Manji

Janssen Research & Development, LLC

David Michelson

Merck Research Laboratories

Patricio O'Donnell

Pfizer Inc.

James Olds

National Science Foundation

Atul Pande

Tal Medical

Steven Paul

Voyager Therapeutics, Inc.

Roderic Pettigrew

National Institute of Biomedical
Imaging and Bioengineering

Emiliangelo Ratti

Takeda Pharmaceuticals International,
Inc.

Todd Sherer

The Michael J. Fox Foundation for
Parkinson's Research

David Shurtleff

National Center for Complementary
and Integrative Health

Paul Sieving

National Eye Institute

Doug Williamson

Lundbeck

Nora Volkow

National Institute on Drug Abuse

Stevin Zorn

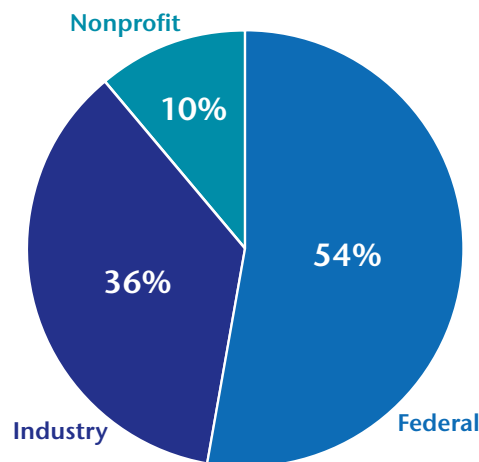
George & Anne Ryan Institute for
Neuroscience and MindImmune
Therapeutics, Inc.

Sponsors

(as of December 2016)

Financial support for the Forum is derived from federal agencies, disease advocacy organizations, industry, and a nonprofit membership society.

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 National Multiple Sclerosis Society
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Timeline

2006 | Establishment **October 4–5** 1st meeting

2007 | **February 26** Biomarkers Workshop | **February 27** 2nd meeting | **April 18** Autism & Environment Workshop | **July 30–31** 3rd meeting | **October 24–25** 4th meeting

2008 | **January 30** 5th meeting | **June 24** 6th meeting | **June 25** Molecules to Mind: Grand Challenges Workshop | **October 3** Venture Philanthropy Strategies Workshop | **October 15–16** 7th meeting

2009 | **Feb 25** 8th meeting | **June 16** Suicidality Workshop | **June 17** 9th meeting | **August 4–5** Uganda Workshop | **October 18** SFN: Social Issues Roundtable | **November 3** 10th meeting | **November 9** Animal Law Workshop

2010 | **March 8–9** Sex Differences Workshop | **June 22** Glutamate Workshop | **June 23** 11th meeting | **July 12** ICAD 2010 Session | **December 10** 12th meeting

2011 | **February 2** 13th meeting | **March 2–3** Neuroscience and the Law Workshop | **July 18** AAIC 2011 Session | **July 26–27** Animal Regulations Workshop | **August 10** 14th meeting | **November 30** 15th meeting

2012 | **March 28** 16th meeting | **March 28–29** Animal Models Workshop | **May 10–11** Neurodegeneration Workshop | **July 11** 17th meeting | **September 4–5** SSA Human Resources Workshop | **October 4–5** Sharing Clinical Research Data Workshop | **November 28** 18th meeting

2013 | **March 5** 19th meeting | **April 8–9** Accelerating Therapeutic Development Workshop | **August 22** Meeting on Developing dMRI Standards | **December 2** 20th meeting

2014 | **January 13–14** SSA Essential Medicines Workshop | **February 18** 21st meeting | **June 17** 22nd meeting | **October 28** 23rd meeting | **November 15** Dry AMD Workshop | **November 16** The Neuroscience of Gaming Session

2015 | **January 13–14** Providing Sustainable Access to Mental Health Care: Kenya Workshop | **January 20–21** Financial Incentives Workshop | **February 24** Cognitive Dysfunction in Depression Workshop | **March 2–3** Non-Invasive Neuromodulation Workshop | **April 28–29** Providing Sustainable Access to Mental Health Care: Ghana Workshop | **June 4–5** 24th meeting | **July 20** Assessing the Impact of Applications of Digital Health Records on Alzheimer's Disease Research Session | **November 10** 25th meeting

2016 | **February 23** 26th meeting | **March 3–4** Neuroscience Trials of the Future Workshop | **June 14–15** 27th meeting and Multimodal Therapies Workshop | **September 12–13** 28th meeting and Therapeutic Development in the Absence of Predictive Animal Models Workshop | **September 15–16** OECD Workshop

2017 | **March 20–21** 29th meeting and Biomarkers of Neuroinflammation Workshop | **September 8** Blood-Brain Barrier Workshop | **October 11–12** 30th meeting and Opportunities and Challenges to Developing Non-Opioid Alternatives for Treating Pain Workshop



About the Neuroscience Forum

The Forum on Neuroscience and Nervous System Disorders at the National Academies of Sciences, Engineering, and Medicine was established in 2006 to bring together leaders from government, industry, academia, disease advocacy organizations, and other interested stakeholders. The Forum meets several times a year and provides its members with a neutral venue for exchanging information, ideas, and differing perspectives. At its meetings, the Forum examines significant—and sometimes contentious—issues concerning scientific needs and opportunities, priority setting, and policies related to neuroscience and nervous system disorders research; the development, regulation, and use of interventions for the nervous system; and related ethical, legal, and social implications. The Forum sponsors workshops (symposia), workshop proceedings, and commissioned papers as additional mechanisms for informing its membership, other stakeholders, and the public about emerging issues and matters deserving scrutiny. Information about past and upcoming meetings is available at the Forum's website, www.nationalacademies.edu/NeuroForum.

National Academies of Sciences, Engineering, and Medicine Staff

Clare Stroud, Ph.D.

Forum Director

Sheena M. Posey Norris, M.S.

Program Officer

Noam Keren, M.A.

Associate Program Officer

Daniel Flynn, M.P.H.

Senior Program Assistant

Andrew M. Pope, Ph.D.

Director, Board on Health Sciences Policy

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The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Marcia McNutt is president.

The **National Academy of Engineering** was established in 1964 under the charter of the National Academy of Sciences to bring the practices of engineering to advising the nation. Members are elected by their peers for extraordinary contributions to engineering. Dr. C. D. Mote, Jr., is president.

The **National Academy of Medicine** (formerly the Institute of Medicine) was established in 1970 under the charter of the National Academy of Sciences to advise the nation on medical and health issues. Members are elected by their peers for distinguished contributions to medicine and health. Dr. Victor J. Dzau is president.

The three Academies work together as the **National Academies of Sciences, Engineering, and Medicine** to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

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