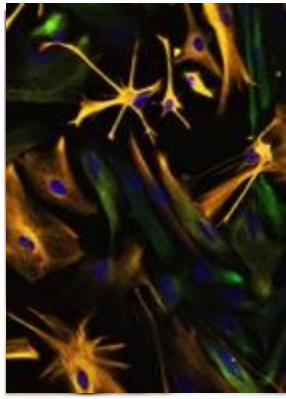
National Institute of Neurological Disorders and Stroke

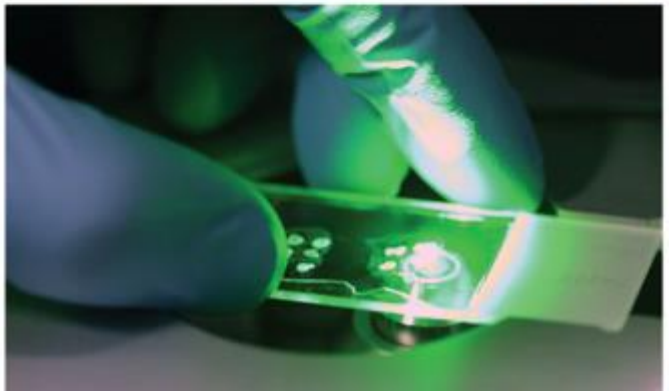
IC Director Report

114th NIH Advisory Committee to the Director

June 9, 2017

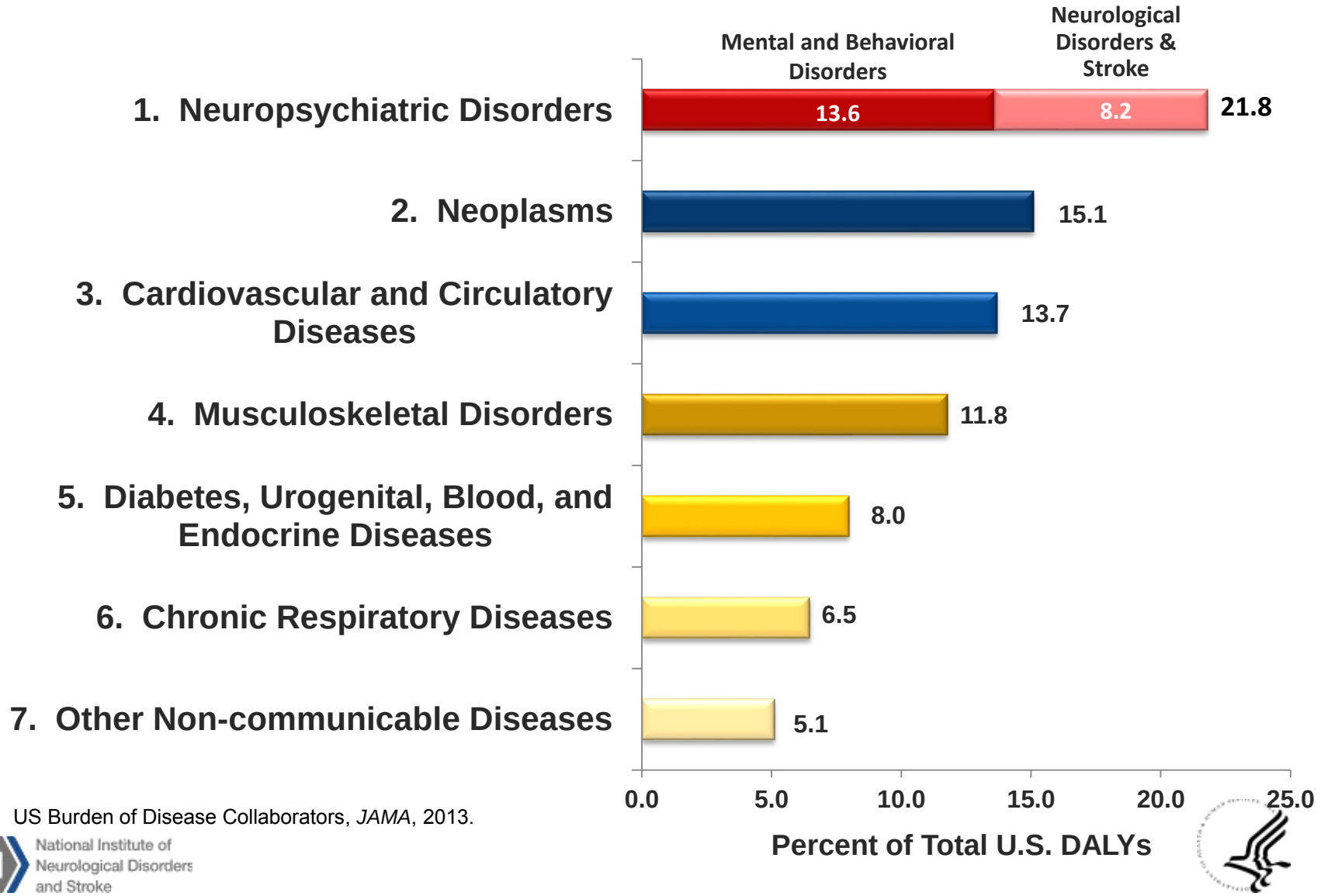
Walter J. Koroshetz, M.D.
Director, National Institute of Neurological Disorders and Stroke, NIH





The Burden of Disease is Substantial

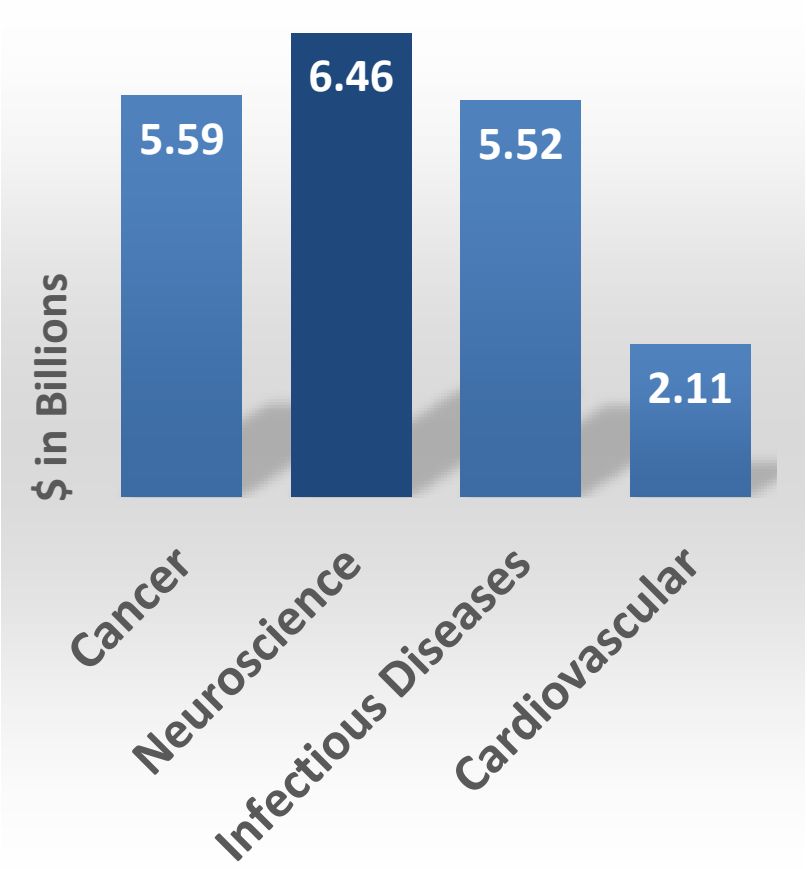
Leading Categories of DALYs 2010: 291 Diseases and Injuries

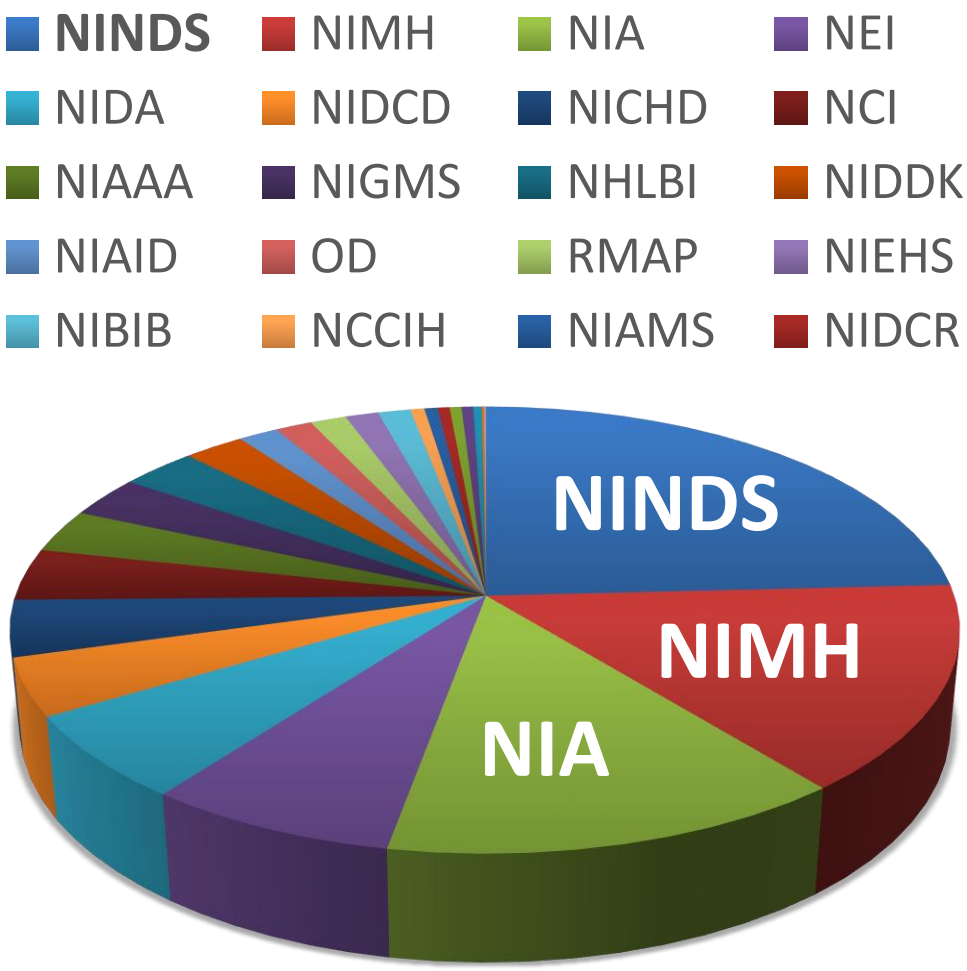


US Burden of Disease Collaborators, *JAMA*, 2013.

NIH National Institute of Neurological Disorders and Stroke

2016 NIH Neuroscience Funding





NIH Blueprint for Neuroscience Research

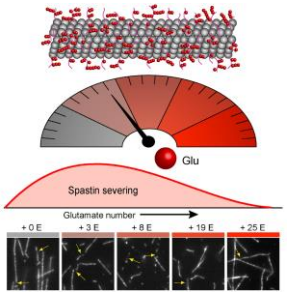
- Launched in 2004, Blueprint is a collaboration among the Office of NIH Director and 13 Institutes and Centers that support research on the nervous system
- Supports development of new tools, training opportunities, and resources for neuroscientists
- Major accomplishments include:
  - Human Connectome Project
  - Blueprint Neurotherapeutics Network
  - Resources and Training Programs
- Next Generation of NIH Blueprint Projects
  - Dynamic Neuroimmune Interactions in the Transition from Brain Function to Dysfunction
  - Novel Technologies for Rapid Characterization of Extracellular Vesicles of Central Nervous System Origin
  - Neurobiology of Small Blood and Lymphatic Vessels in Health and Disease

The NIH Office of the Director and these NIH Institutes and Centers participate in the NIH Blueprint for Neuroscience Research:

- NCCAM
- NEI
- NIA
- NIAAA
- NIBIB
- NICHD
- NIDA
- OBSSR
- NIDCR
- NIEHS
- NIGMS
- NIMH
- NINDS
- NINR

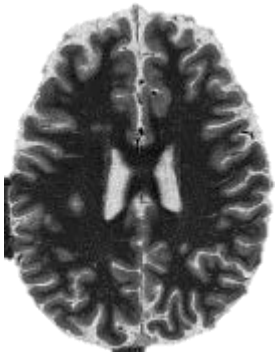
http://neuroscienceblueprint.nih.gov/

Intramural NINDS & Porter Neuroscience Center



Cell

Graded Control of Microtubule Severing by Tubulin Glutamylation



ORIGINAL ARTICLE

The Role of *PIEZO2* in Human Mechanosensation

Alexander T. Chesler, Ph.D., Marcin Szczot, Ph.D., Diana Bharucha-Goebel, M.D., Marta Čeko, Ph.D., Sandra Donkervoort, M.S., C.G.C., Claire Laubacher, B.A., Leslie H. Hayes, M.D., Katharine Alter, M.D., Cristiane Zampieri, Ph.D., Christopher Stanley, M.S., A. Michelle Innes, M.D., Jean K. Mah, M.D., Carla M. Grosmann, M.D., Nathaniel Bradley, B.S., David Nguyen, B.S., A. Reghan Foley, M.D., Claire E. Le Pichon, Ph.D., and Carsten G. Bönnemann, M.D.

SCIENCE TRANSLATIONAL MEDICINE

ONCHOCERCIASIS

Nodding syndrome may be an autoimmune reaction to the parasitic worm *Onchocerca volvulus*

Tory P. Johnson,[1] Richa Tyagi,[1] Paul R. Lee,[1] Myoung-Hwa Lee,[1] Kory R. Johnson,[2] Jeffrey Kowalak,[3] Abdel Elkahloun,[4] Marie Medynets,[5] Alina Hategan,[1] Joseph Kubofcik,[6] James Sejvar,[7] Jeffrey Ratto,[8] Sudhir Bunga,[8] Issa Makumbi,[9] Jane R. Aceng,[9] Thomas B. Nutman,[6] Scott F. Dowell,[10] Avindra Nath[1]*

Porter Neuroscience Research Center - home to scientists from 10 different ICs

- Brings together over 800 scientists in 85 laboratories

Major research institution, with roughly:

- 50 Principal Investigators/Senior Staff
- 65 Staff Scientists/Staff Clinicians
- 250 Fellows
- Joint Residencies in Neurology, Neurosurgery, Neurophysiology, Stroke

Highly productive:

- ~130 active clinical protocols
- ~350 papers published or in press each year
- 100's of license agreements and patents
- Cutting-edge imaging facilities

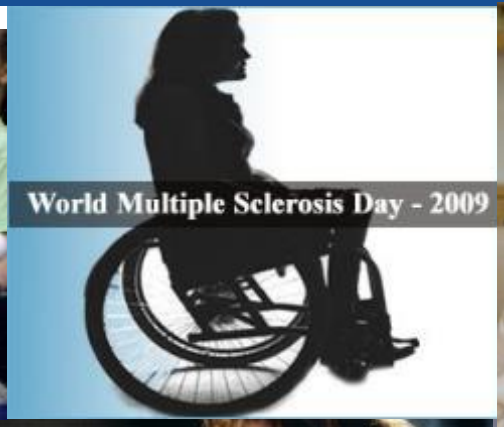
The National Institute of Neurological Disorders and Stroke (NINDS)

The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease.

Strategies:

- Invest across the full spectrum of basic, translational, and clinical research
- Establish a data-driven process to identify unmet scientific opportunities and public health needs within and across neurological diseases
- Support research resources and technical advances that catalyze new discoveries
- Communicate and collaborate with the public and with others involved in biomedical research
- Train a robust and diverse neuroscience research workforce
- Adopt a culture of evaluation and continuous improvement across all NINDS programs

The Challenges are Many



A new study from Nancy Wexler, in Venezuela in the 1990s
with a boy with Huntington's disease, suggests there may
ways to delay the onset of the disease.

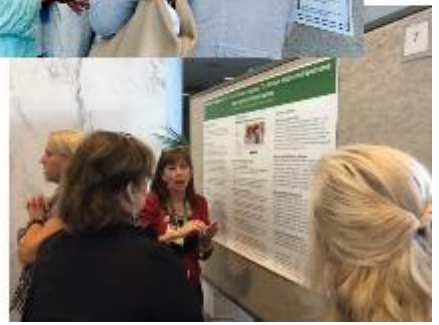
Engaging with Patients: NINDS Nonprofit Forum

2016 Progress through Partnership Forum provided an opportunity for nonprofit leaders to network with colleagues and engage with NINDS staff

Featured panel discussions on:

- natural history databases
- biomarker identification
- data integration and management
- clinical outcome measures, and
- success stories

New record for registration: 161 registrants, including 107 representatives from 87 patient groups



Poster session with NPOs and NINDS staff

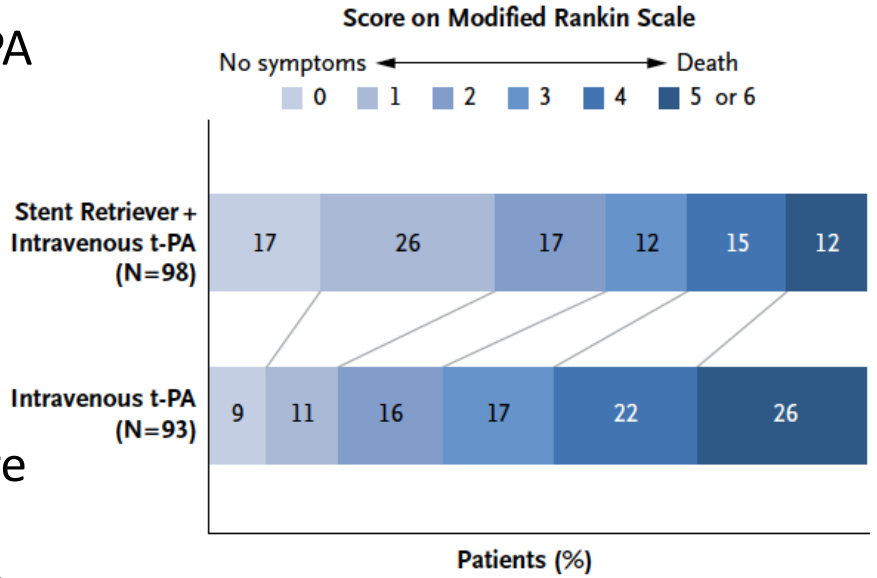
Some BIG Leaps Forward in Treating Neurologic Disorders. No Longer "Diagnose and Adios"!

- **Stroke death rates** have dropped more than 70% since 1960's
- Reperfusion therapy for **acute stroke** transformed the country's care of stroke patients.
- Multiple disease-modifying therapies for **multiple sclerosis** now available, even an oral medication.
- Wide variety of **anti-seizure medications** now available.
- In addition to drugs for **Parkinson's disease**, and then deep brain stimulation for when medications are no longer consistently beneficial.
- Treatment to stop or reverse **migraine attacks**.
- Gene replacement for some **rare childhood disorders**.
- Brain and spinal cord **neuroimaging** has revolutionized neurology and neurosurgery.

Revolutionary Advance in Acute Stroke Therapy: Intra-Arterial Revascularization

2015 Endovascular therapy trials

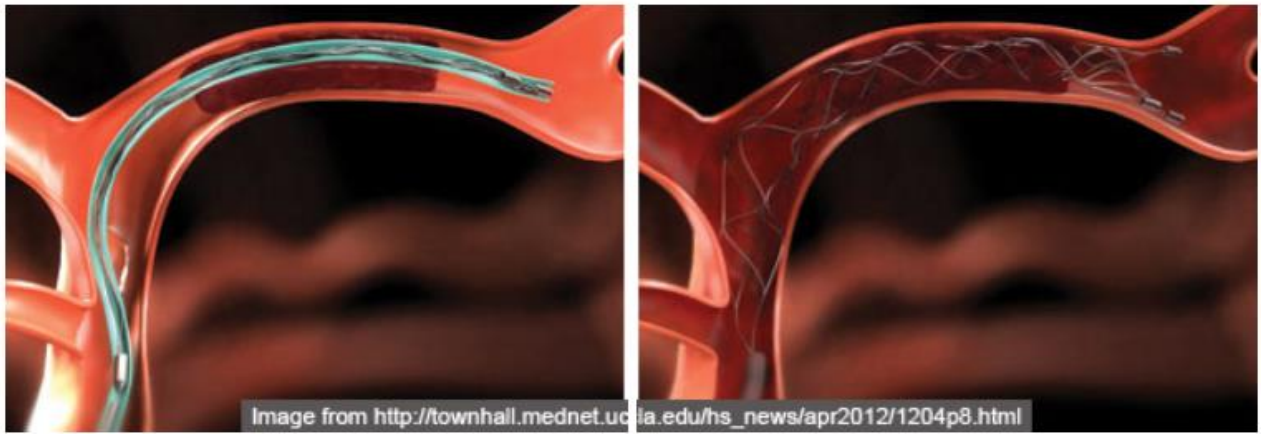
- Endovascular therapy plus intravenous tPA highly beneficial, compared to tPA alone
  - ➢ Number needed to treat as low as 3



SWIFT PRIME
N Engl J Med 2015; 372:2285-2295.

Prior trials (NINDS-funded Interventional Management of Stroke-3 (IMS3)) failed to show benefit – what changed?

- Newer stent-retriever technology → more complete recanalization
- Ability to achieve rapid time to treatment
- Neuroimaging criteria for selecting patients



FDA Approvals in Past Year

Batten's disease

– Cerliponase alfa (Brineura), a recombinant form of the enzyme TPP1, the enzyme deficient in patients with CLN2 disease

Cluster headache

– GammaCore, a vagal nerve stimulation device

Multiple Sclerosis

– Ocrelizumab (Ocrevus), a monoclonal Ab against CD20 B lymphocytes

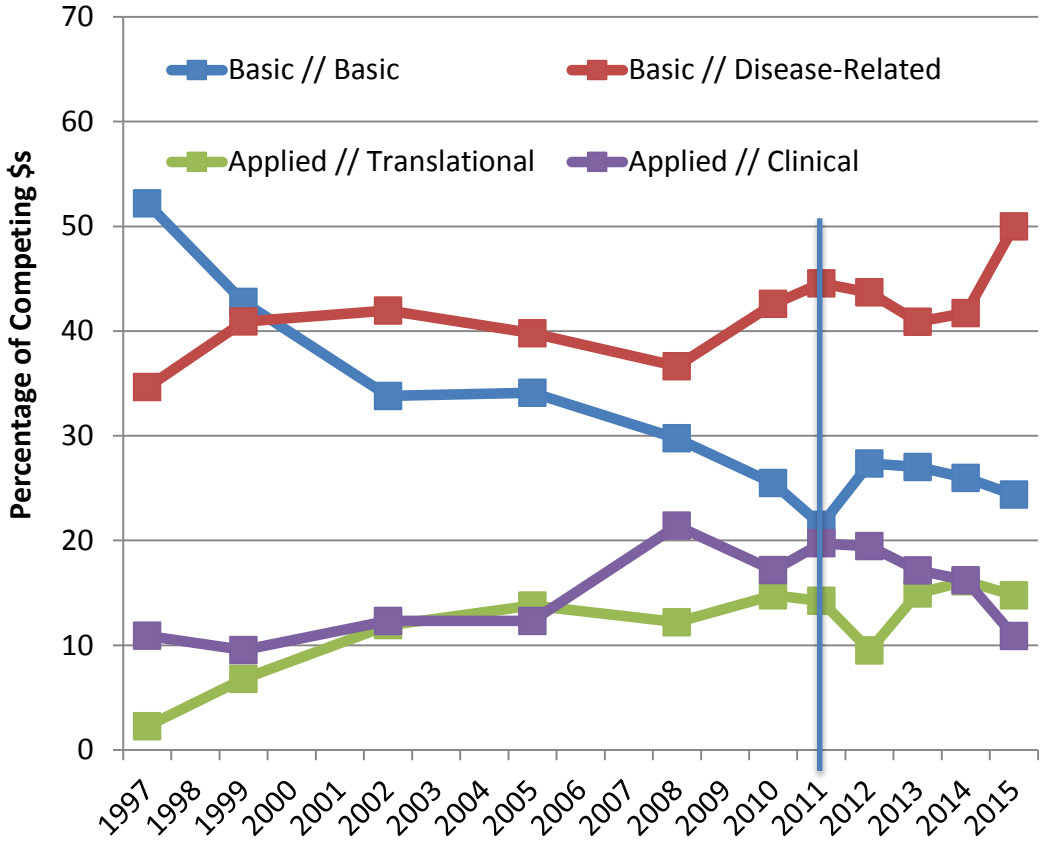
Amyotrophic Lateral Sclerosis (ALS)

– Endaravone (Radicava), a free radical scavenger

Spinal Muscular Atrophy (SMA)

– Nusinersen (Spinraza), an antisense oligonucleotide therapy that increases SMN protein

NINDS Portfolio & Support of Basic Science



- NINDS regularly analyzes research funding trends
- '05-'11 Fundamental neuroscience funding dramatically decreasing
  - Due to decrease in # of applications
  - Applications do better in review
- RFA: Promoting Research in Basic Neuroscience (R01)
  - Goal: to stimulate increased research applications addressing fundamental questions in basic neuroscience

LETTERS

Science

Basic science: Bedrock of progress

Francis S. Collins[1,*], James M. Anderson[2], Christopher P. Austin[3], James F. Battey[4], Linda S. Birnbaum[5], Josephine P. Briggs[6], Janine A. Clayton[7], Bruce Cuthbert[8], Robert W. Eisinger[9], Anthony S. Fauci[10], John I. Gallin[11], Gary H. Gibbons[12], Roger I. Glass[13], Michael M. Gottesman[14], Patricia A. Gray[15], Eric D. Green[16], Franziska B. Greider[17], Richard Hodes[18], Kathy L. Hudson[2], Betsy Humphreys[19], Stephen I. Katz[20], George F. Koob[21], Walter J. Koroshetz[22], Michael S. Lauer[23], Jon R. Lorsch[24], Douglas R. Lowy[25], John J. McGowan[26], David M. Murray[27], Richard Nakamura[28], Andrea Norris[29], Eliseo J. Perez-Stable[30], Roderic I. Pettigrew[31], William T. Riley[32], Griffin P. Rodgers[33], Paul A. Sieving[34], Martha J. Somerman[35], Catherine Y. Spong[36], Lawrence A. Tabak[1], Nora D. Volkow[37], Elizabeth L. Wilder[38]

Rigor, not Mortis

"Scientific rigor is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. This includes full transparency in reporting experimental details so that others may reproduce and extend the findings."

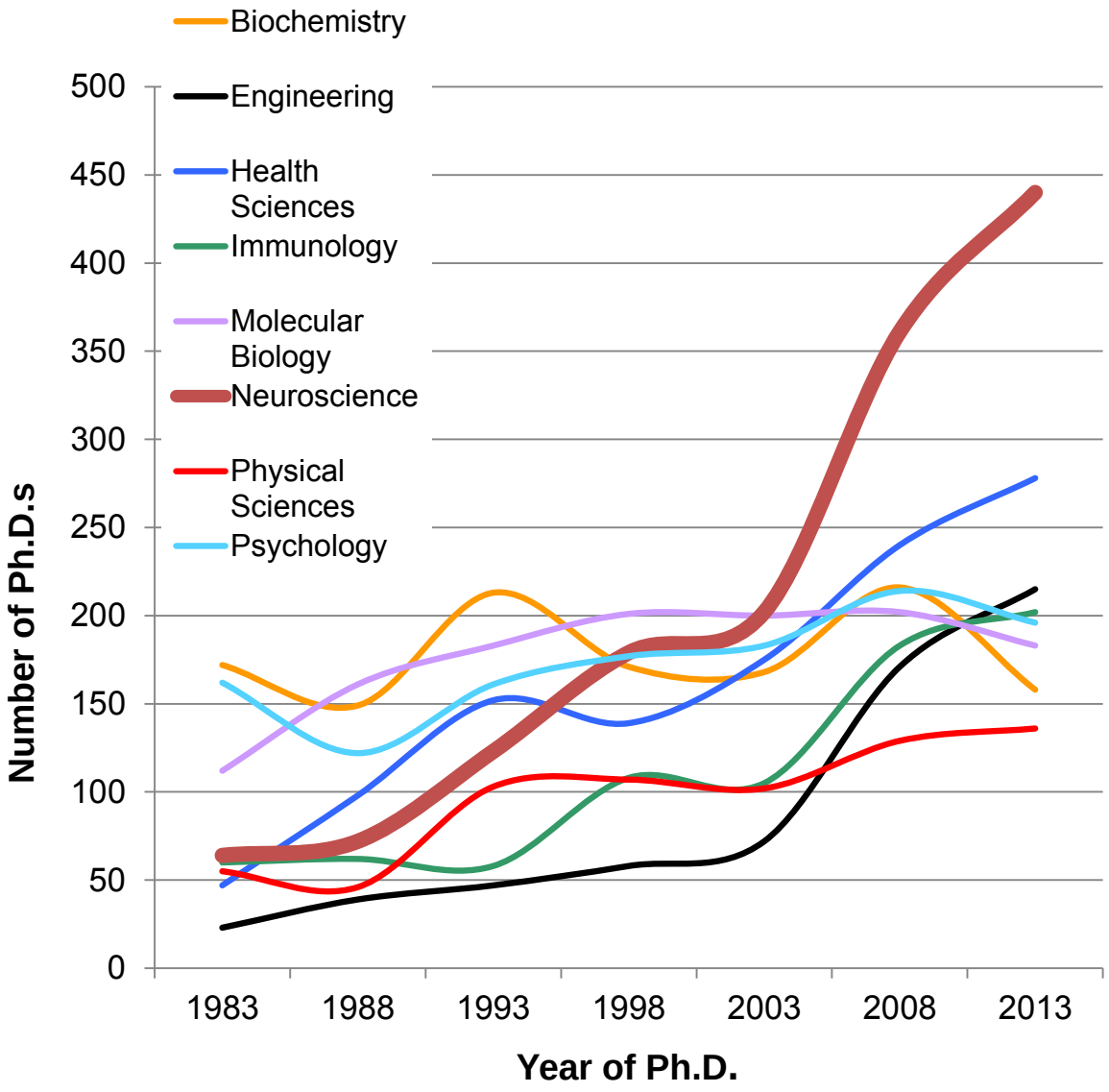
- NIH and NINDS focus on improving the quality and rigor of research that is funded
- 2011 NINDS Notice: "increasing awareness among neurological disease communities that the predictive value of preclinical research is improved when information is made available about study design, execution, analysis and interpretation"
- NINDS staff have given 80+ presentations over the past 4 years to encourage rigor
- NINDS recently created the Office of Research Quality, led by Dr. Shai Silberberg, to advise leadership on issues related to rigor, transparency and quality of research

"Scientific inquiry must be pursued with an exacting attention to experimental design and a focus on robust, reproducible results that is matched by transparency in reporting"

NINDS Research Program Award (R35)

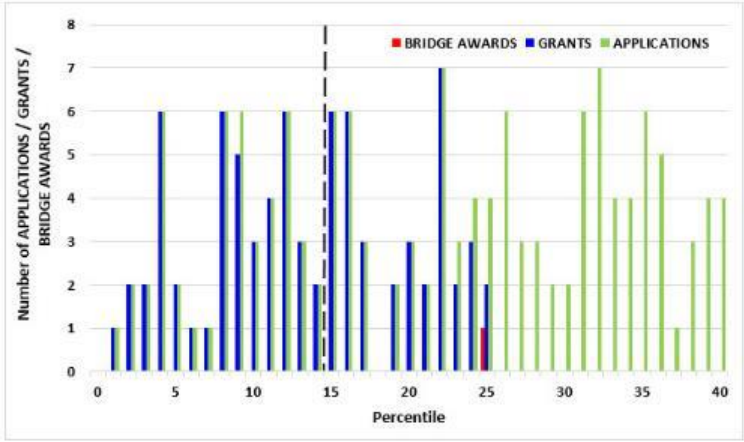
- Program Goals
  - Provide sustained and flexible support
  - Allow investigators freedom to pursue longer range, innovative, or high-risk research
  - Reduce time writing multiple applications
- Award Features:
  - 8 year award
  - Up to $750K/year direct cost
  - Requires 50% effort
  - Applicant must have 5 years R01-equivalent support
- First Round of Awards: 30 grants, ~$25M, 15% funding rate

Neuroscience is a Young and Growing Discipline and ESI Support is Strong



Success rates for NINDS ESI applicants approach 29%

NINDS funds ESI 10 pts above payline



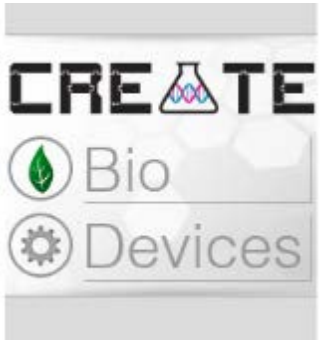
NINDS R25:
Research Support for Residents and Fellows

Neurology, Neurosurgery, Neuroradiology Neuropathology, Neuroanasthesia and Emergency Medicine

- Institutional award started in 2009
- PGY salary commensurate with effort and $3,000 for travel
  - Funds 6-12 months during residency
  - If completed appropriately, up to 2 more years in residency or fellowship
  - 80% effort required while supported (surgeons can go to 50% effort after 1 year of support)
- Mandatory attendance at workshop – career development, networking, one-on-one help with specific aims, poster session

Goal and metric of success: ***Get to a K award***

NINDS Division of Translational Research



Goal: advance promising therapies to hand-off to biotech/pharma

- Innovation Grants to Nurture Initial Translational Efforts (IGNITE)
  - Early-stage therapy development
  - Four separate opportunities from assay development to platform technology development
- Blueprint Neurotherapeutics Network
  - Development of small molecules
  - Provides investigators with access to consultants and contracts that provide discovery, preclinical development, and clinical trial support
- CREATE (Cooperative Research to Enable and Advance Translational Enterprises)
  - Development of biologics (including proteins, peptides, nucleic acids, gene and cell therapies)
  - Development of devices (including implants, stents, and prosthetics)

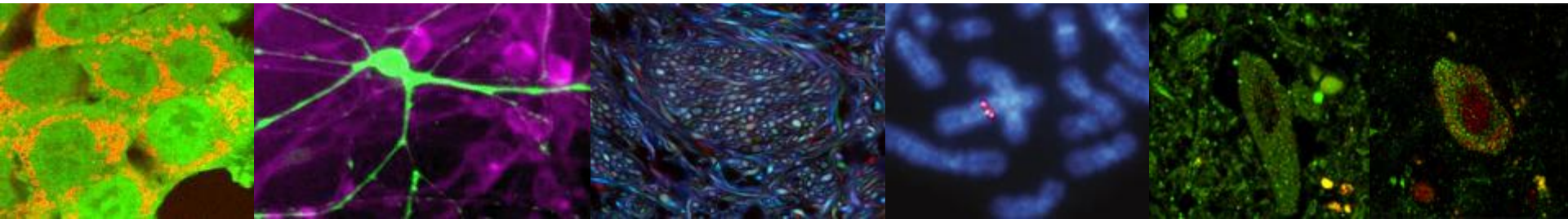
These programs:

- Are milestone driven
- Offer multiple entry points and seamless path of support across the therapy development pipeline

Accelerated Medicines Partnership in Parkinson's Disease (AMP-PD)

Public Private Partnership to identify and validate diagnostic, prognostic, and progression biomarkers

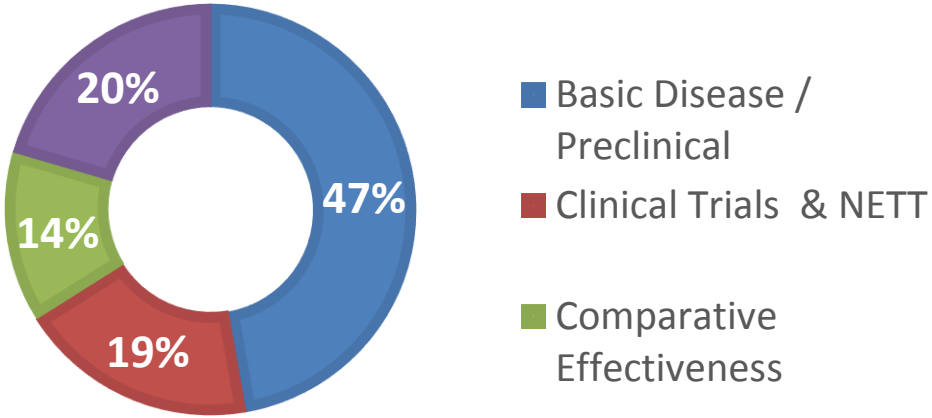
- **Projected Outcomes:** Improvement in clinical trial design, patient stratification, monitoring of disease progression, identification of therapeutic targets
- **Project aims to:**
  - Standardize data collection for biomarkers in multiple cohorts
  - Conduct standardized assays on thousands of existing biosamples, as well as incorporating existing clinical, imaging, and genetic data
  - Pursue additional large-scale biomarker discovery with transcriptomics, epigenomics, whole genome sequencing, metabolomics, proteomics
- **Partners:** GSK, MJFF, Pfizer, Sanofi, Verily, ~$2m/yr NINDS match w/private support



Traumatic Brain Injury

- **Large prospective data collection efforts:**
  1. Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) together with EU's CENTER TBI to tailor therapy
  2. Approaches and Decisions in Acute Pediatric TBI Trial (ADAPT) trials to understand most effective treatments
- Strategies to Innovate EmeRgENcy Care Clinical Trials (SIREN) network for **phase III trials**
- **Common data elements** in TBI for preclinical and clinical research and data repository in concert with DOD
- **Chronic traumatic encephalopathy:** Pathologic and Clinical characterization
- **Childhood concussion**

Percent of Total NINDS TBI Expenditures



TRACK-TBI
Transforming Research and Clinical Knowledge in Traumatic Brain Injury
International Traumatic Brain Injury Research Initiative

FITBIR
Federal Interagency Traumatic Brain Injury Research
INFORMATICS SYSTEM

adapt
Approaches and Decisions in Acute Pediatric TBI Trial

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

More than one million Americans have ME/CFS, a debilitating disease that lacks a universally accepted case definition, cause, diagnosis, or treatment

NIH-wide intramural study is underway

- Focus on understanding the clinical and biological characteristics of ME/CFS
- Study enrolled healthy volunteers, people with ME/CFS

FOAs issued in January 2017 for Collaborative Research Centers and Data Management and Coordinating Center

- Building a foundation for ME/CFS research
- Coordinated by trans-NIH ME/CFS working group, a trans-NIH effort involving many ICs

Common Data Elements for ME/CFS research

- Collaboration with CDC to establish standards for data collection and analysis

ME/CFS featured in the NIH Director's Blog

- Part of NIH's continuing efforts to engage with the ME/CFS community

NIH Office of Pain Policy and the NIH Pain Consortium: Advancing Pain Research

The government's first broad-ranging effort to improve how pain is perceived, assessed, and treated—a significant step toward the ideal state of pain care.

National Pain Strategy

A Comprehensive Population Health Level Strategy for Pain

Coordinated roadmap toward improving US pain care in:

- population research;
- prevention and care;
- disparities;
- service delivery and payment;
- training and professional/public education

NIH coordinating trans-Agency implementation

Federal Pain Research Strategy

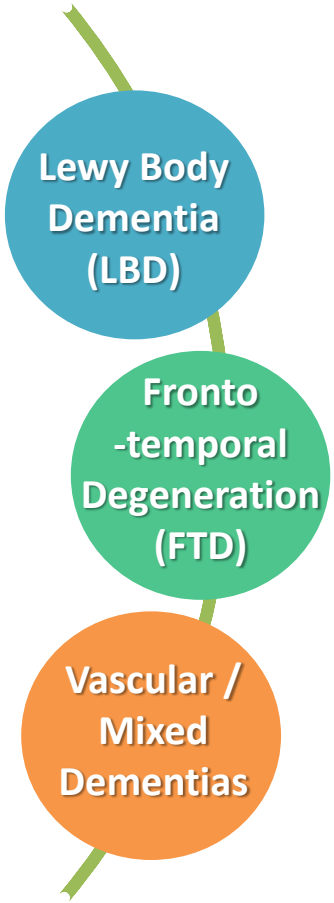
NIH Pain Research @NIHPainResearch

https://iprcc.nih.gov

The Interagency Pain Research Coordinating Committee

Alzheimer's Disease-Related Dementias (ADRD)

ADRD: Types of dementias that share cognitive and pathological features with Alzheimer's and/or commonly co-occur with typical Alzheimer's pathology



National Alzheimer's Project Act (NAPA)

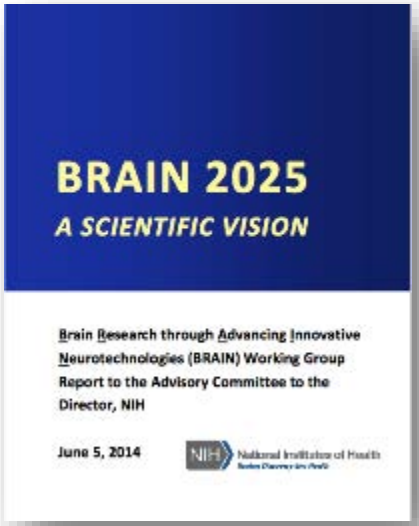
- *NINDS leads ADRD research summits to identify priorities*
- Funded three projects investigating the **Mechanistic Basis of Diffuse White Matter Disease** in Vascular Contributions to Cognitive Impairment and Dementia
- Established **a small vessel VCID Biomarkers Consortium** to develop biomarkers for cerebrovascular disease for use in clinical trials
- Created **a multi-center, interdisciplinary "Center without Walls"** to study molecular mechanisms that lead to FTD
- Supporting **discovery of FTD-causing genetic mutations**
- **Supporting biomarker discovery studies for LBD**
- Identifying biological, behavioral, sociocultural, and environmental **factors that influence health differences in AD/ADRD**

Mind Your Risks℠

www.mindyourrisks.nih.gov

THE BRAIN INITIATIVE®

Focus on Circuit Structure and Function



Goal: See the circuits in action to understand:

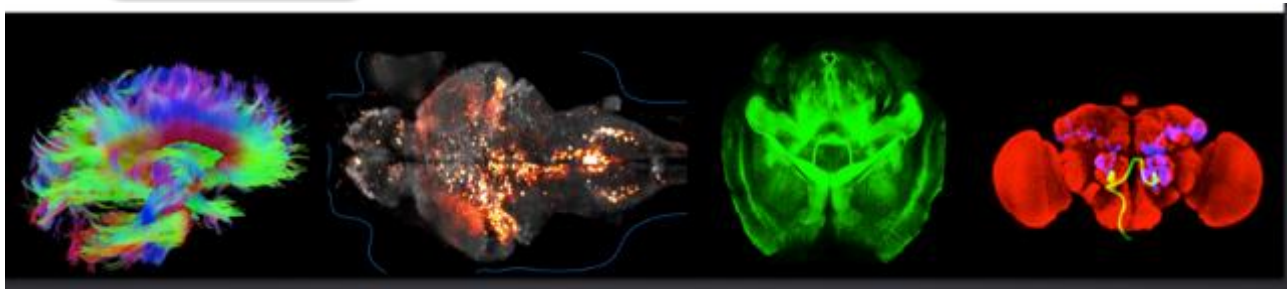
- How the brain plans, executes, learns, and remembers
- How to monitor/manipulate circuits for improved function
- That disordered brain circuits cause neuro/mental/substance use disorders

Long-term goal: Make circuit abnormalities the basis of diagnostics, and normalization of circuit function the target of intervention

FIRST FIVE YEARS — Emphasize technology development

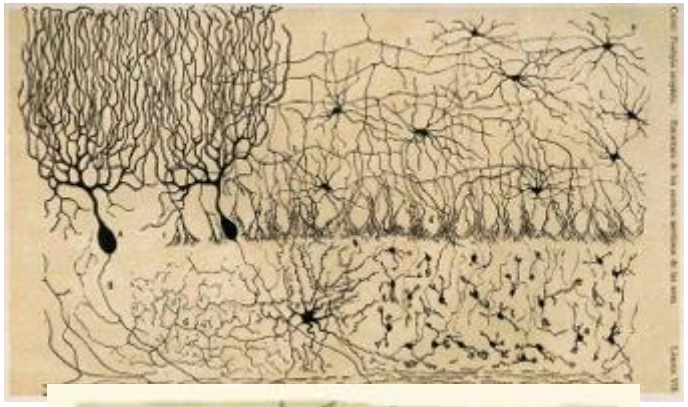
SECOND FIVE YEARS — Emphasize discovery driven science

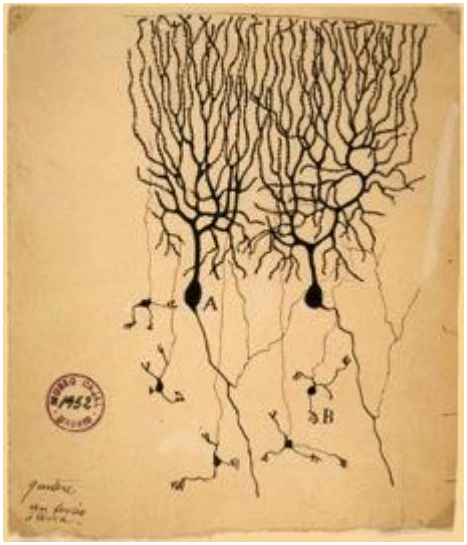
Molecular/Structural Pathology → **Circuit Dysfunction** → **Neuro/Mental/Substance Abuse Functional Disability**



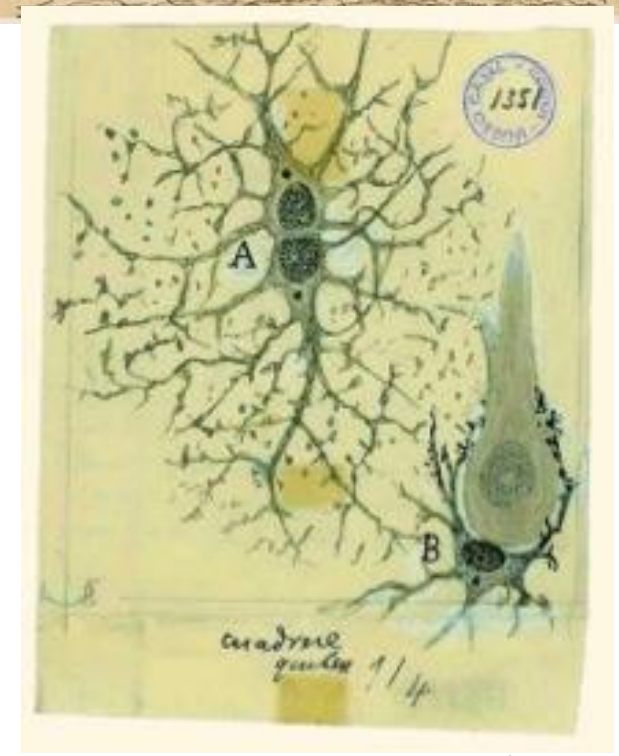
NIH National Institutes of Health
Turning Discovery Into Health

Golgi Stain Drawings by Ramón y Cajal



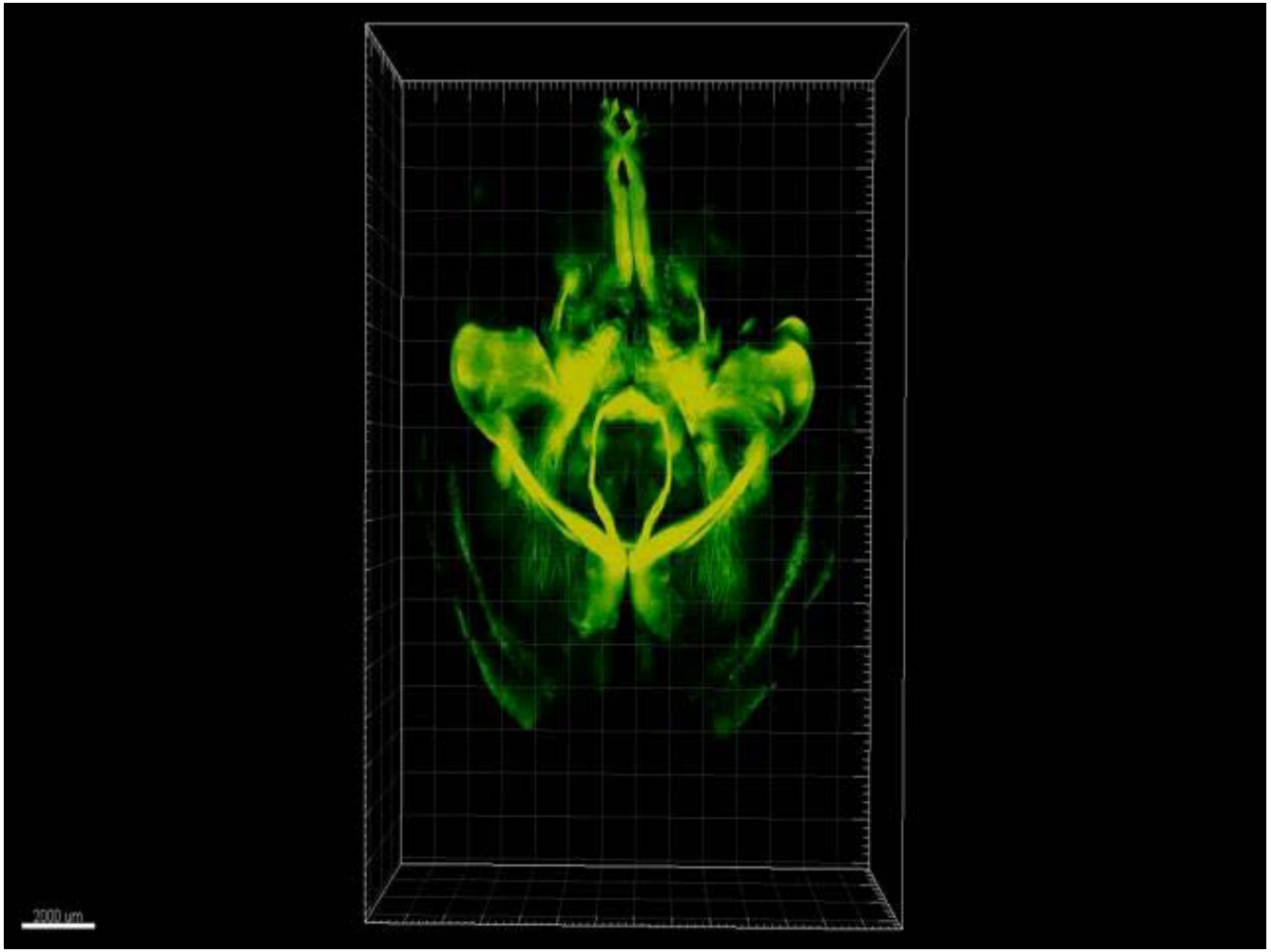


John Edward Porter Neuroscience Research Center



Made possible through a scientific partnership established in 2015 with the Cajal Institute in Madrid

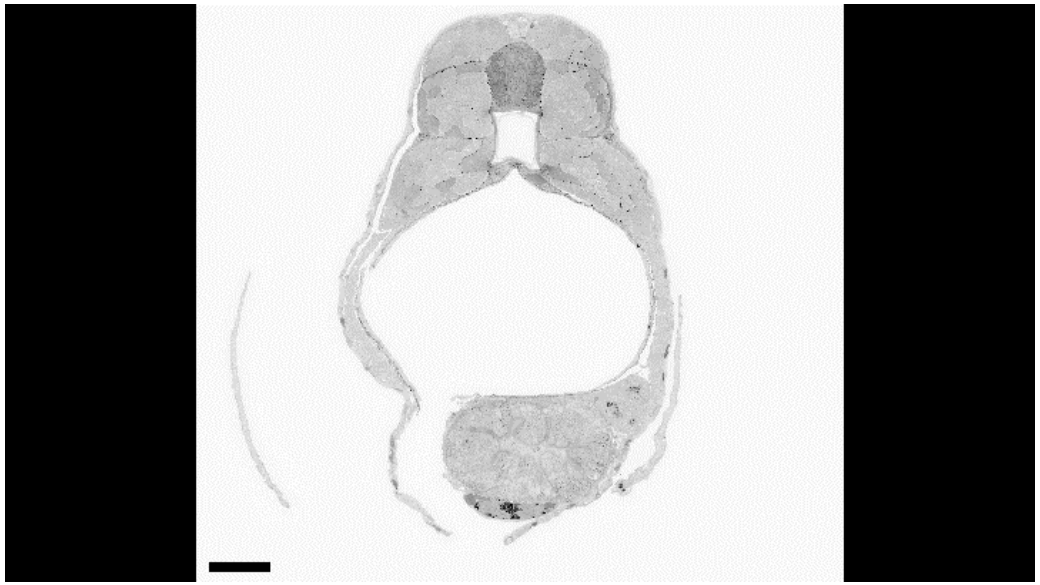
CLARITY: *Neuroanatomy for the 21st Century*

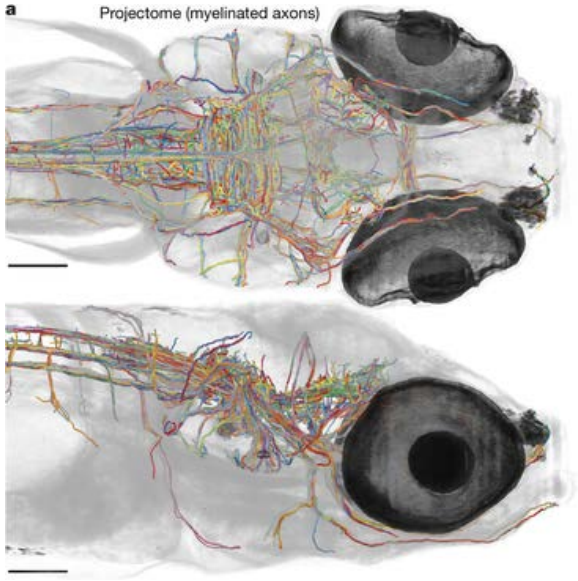


https://www.youtube.com/watch?v=EI-VcvwgCgE

Deisseroth *et al*, Stanford

First EM Resolution Map of a Verebrate Brain

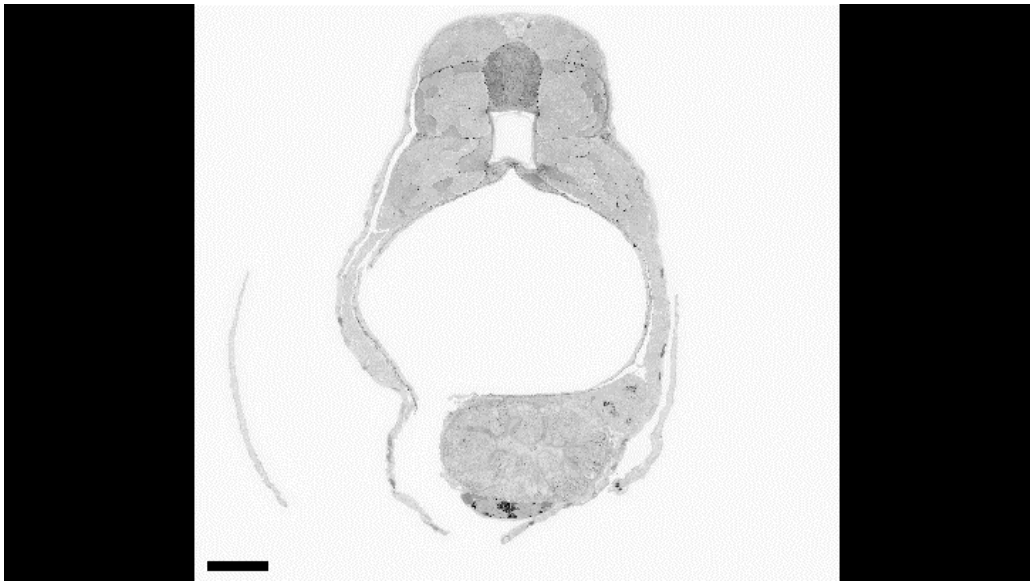


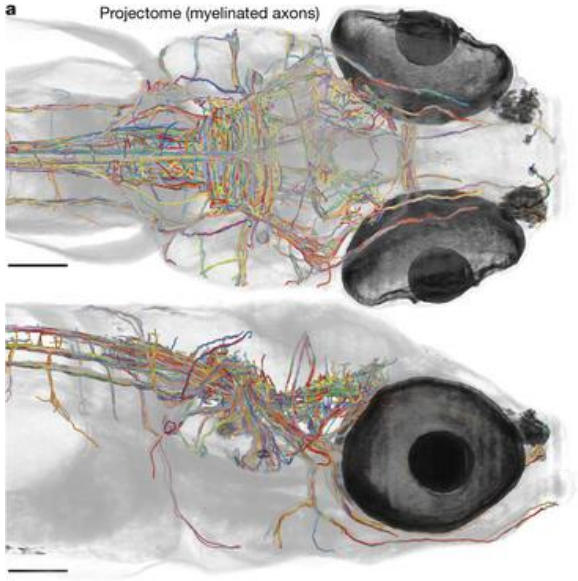


Hildebrand et al., *Nature,* 2017

- BRAIN Investigator Florian Engert's group reveals whole-brain ssEM data for the complete brain of a larval zebrafish at 5.5 days post-fertilization
- Multiple rounds of targeted imaging at different scales reduced acquisition time and data management requirements
- Allows for reconstruction of all myelinated axons (projectome)
- Open-access resource is available for the scientific community

First EM Resolution Map of a Verebrate Brain





Hildebrand et al., *Nature,* 2017

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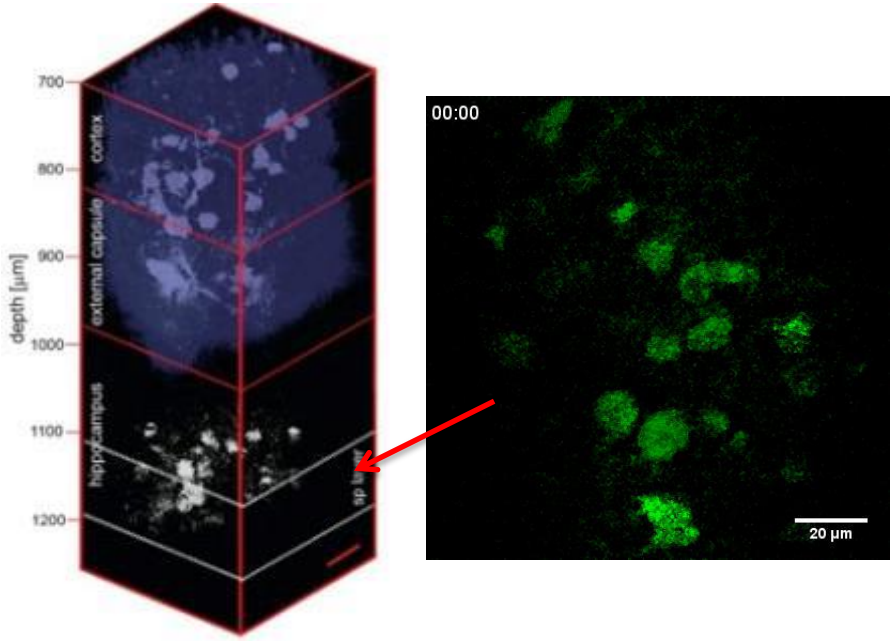
Over 200 publications have emerged from NIH BRAIN to date

Optical Instrumentation

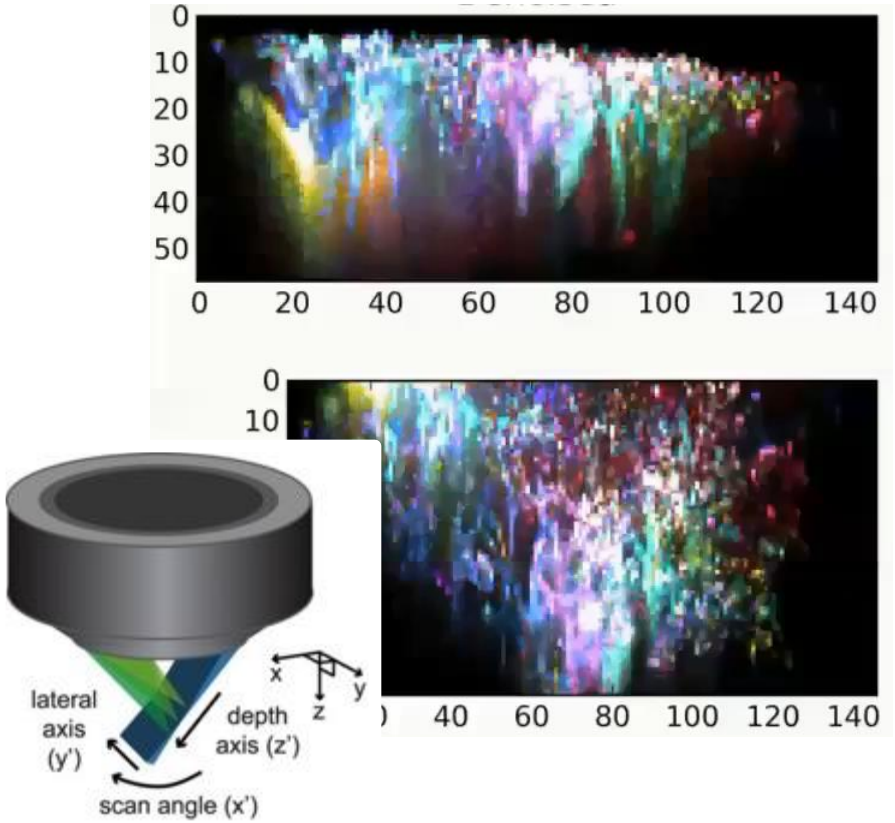
***Deeper*: anywhere in the brain**

***Faster*: whole volumes rather than single plane**

More precise targeting during behavior



3-photon imaging of hippocampal neurons >1mm deep in the mouse brain – *Cornell (Chris Xu)*

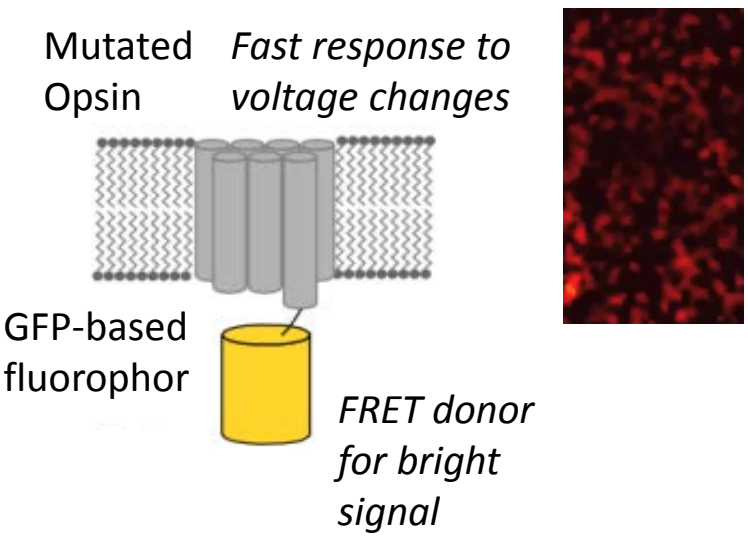


SCAPE imaging of cortical neurons colored by deconvolution – *Columbia (Elizabeth Hillman, Liam Paninski)*

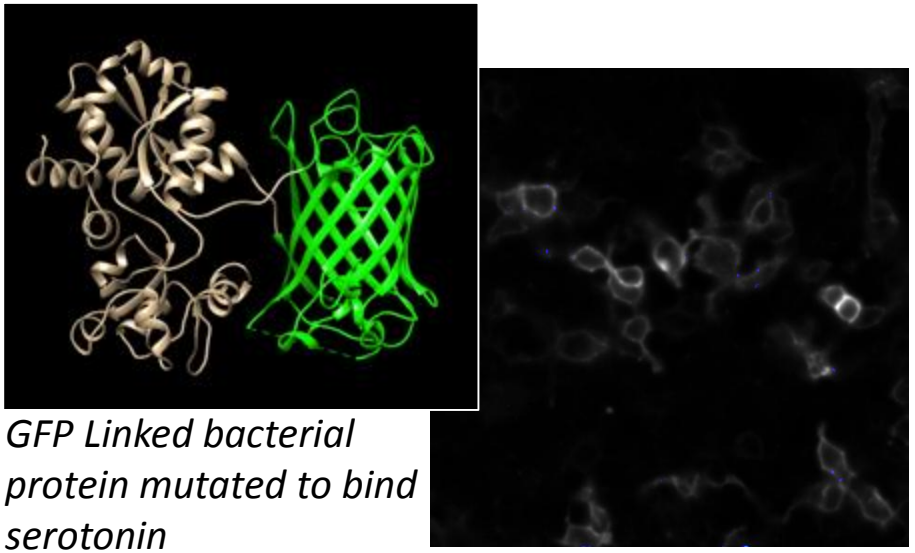
Probe Development

***Sensors*: for voltage, transmitters/modulators, activity history, activated synapses, MRI, calcium**

***Activators/inhibitors*: chemical-genetic, photo-switchable ligands, signaling, synaptic plasticity**



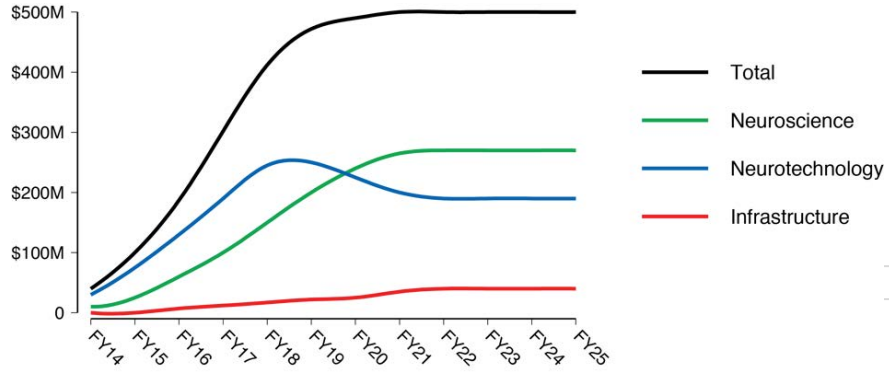
Voltage imaging of single neuron dynamics in mouse cortex in vivo – *Stanford (Mark Schnitzer/Michael Lin)*



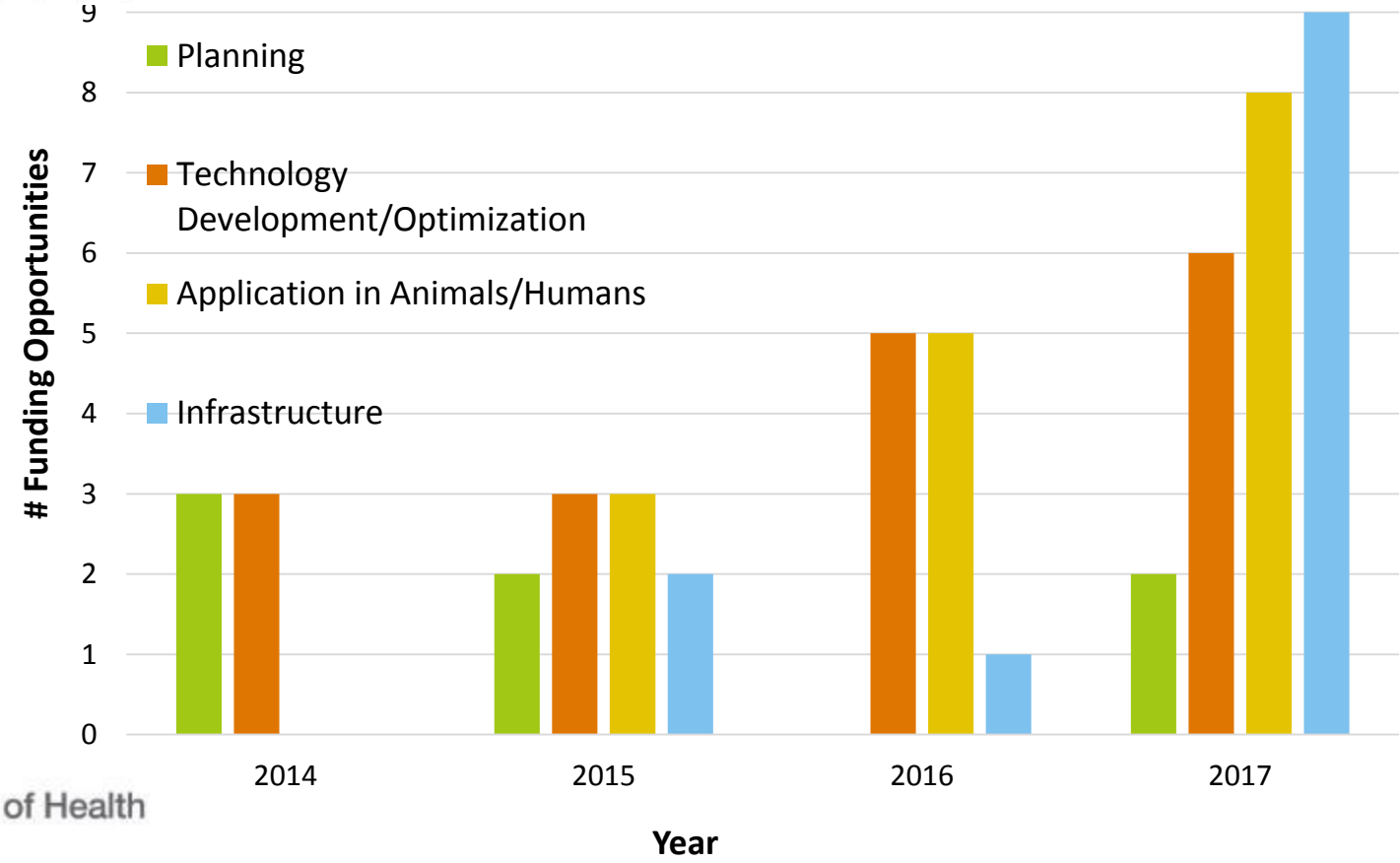
GFP Linked bacterial protein mutated to bind serotonin

New optogenetic serotonin sensor with high SNR in cultured cells – *UC Davis (Lin Tian)*

Circuit Maps, Tools and Knowledge



***BRAIN 2025* Report**: First years [should] emphasize technology development and validation, with a growing emphasis on problem-driven neuroscience after FY2020



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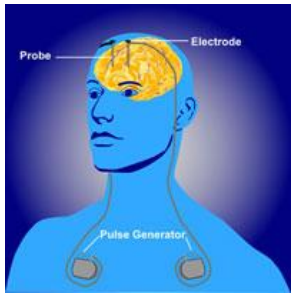
BRAIN Funded Awards: *Human Neuroscience*

Funding Opportunity	FY 2014	FY 2015	FY 2016
Next-Gen Human Imaging	9	6	12
Next-Gen Human Invasive Devices	-	3	8
Non-Invasive Neuromodulation	-	-	16 (7 in humans)

BRAIN investment in human neuroscience projects increases each year

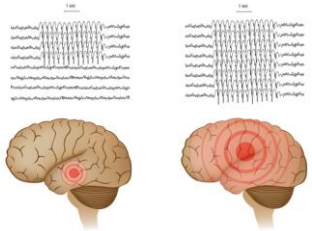
Current projects focus on human disorders including:

Parkinson's Disease
Obsessive Compulsive Disorder

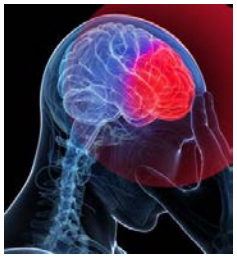


Blindness

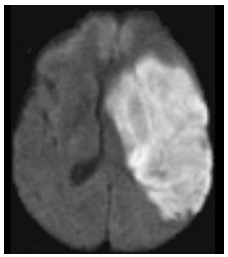
Epilepsy



Traumatic Brain Injury



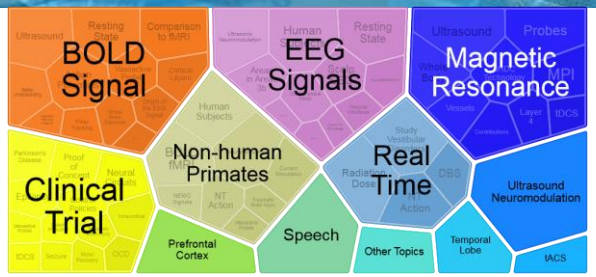
Stroke



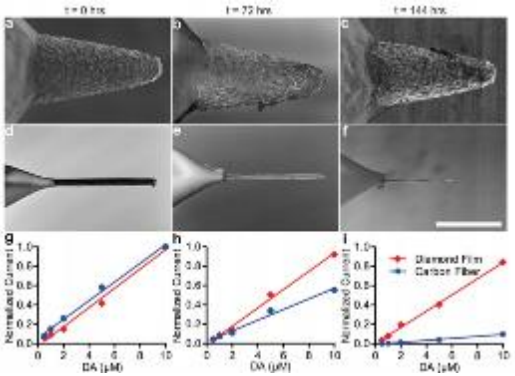
NIH National Institutes of Health
Turning Discovery Into Health

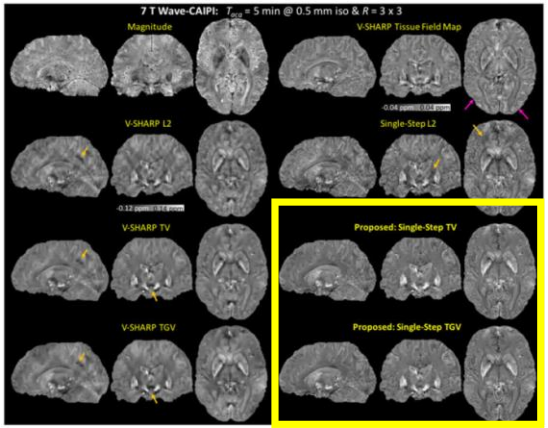
Technological Advances: *Human Applications*

Current projects focused on advancing human neuroscience incorporate:



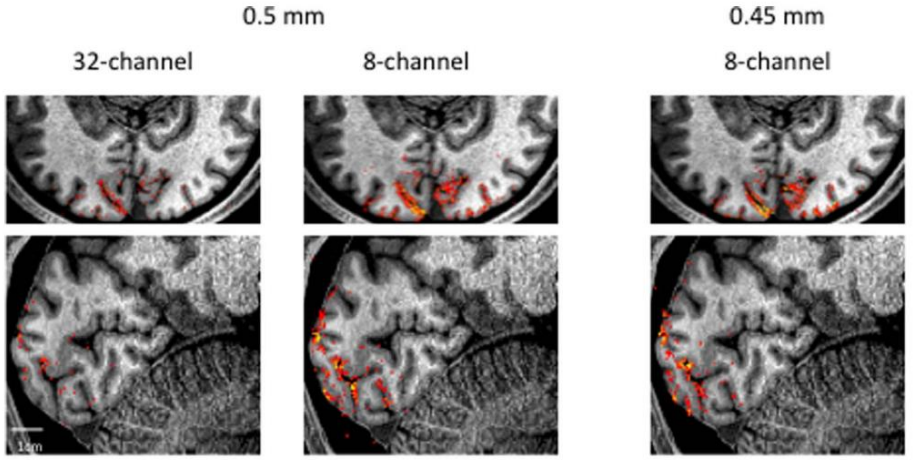
Diamond electrodes can measure stimulation-driven monoamine transmitter release in basal ganglia of humans with greater longevity and strength Bennet et al., *Frontiers in Human Neuroscience,* 2016





New single-step processing technique reduces error, creating high-quality MRI images with less blurring

Chatnuntawetch et al., 2017



New 8-channel magnetic receiver captures higher-resolution images of brain activity in human visual system Feinberg et al., 2017

Thank You!

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Director

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Recruiting Outstanding Workforce: *Engaging Many Disciplines*

Department Category (for Contact and Multi PIs)	FY15	~FY16
Biochemistry	11	12
Biology/cell biology/Microbiology/Pathology/Immunology	43	36
Chemistry	17	11
Genetics	4	3
Biostatistics/math/computer science	12	33
Physics	16	14
Engineering (all categories)	119	141
Neuroscience/ Neurology	146	141
Neurosurgery	14	47
Psychiatry/Psychology	17	69
Radiology/ Radiation-Diagnostic	31	61
Bioimaging/ Imaging	15	8

Recruiting Outstanding Workforce: *New, Early Stage Investigators*

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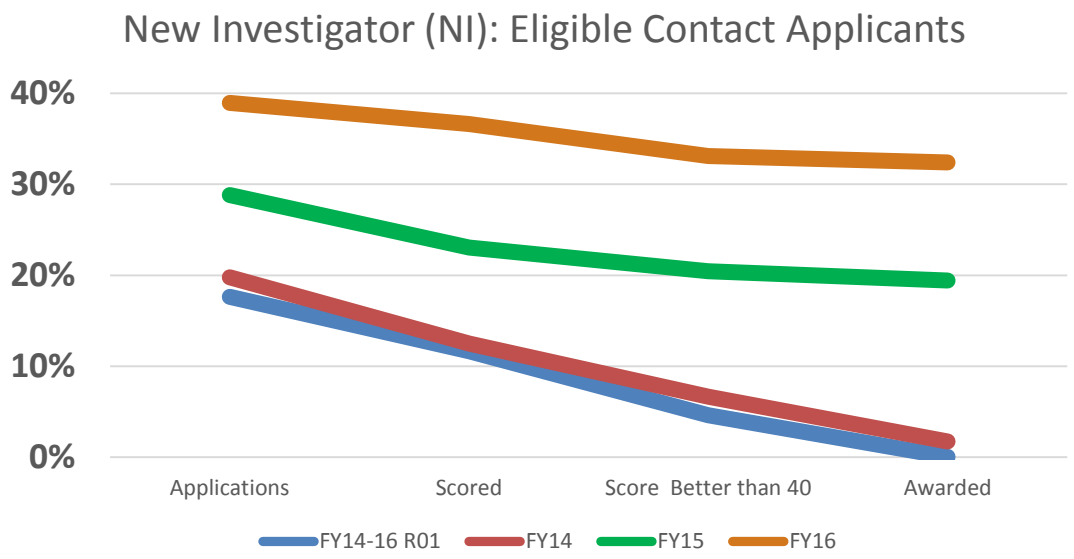
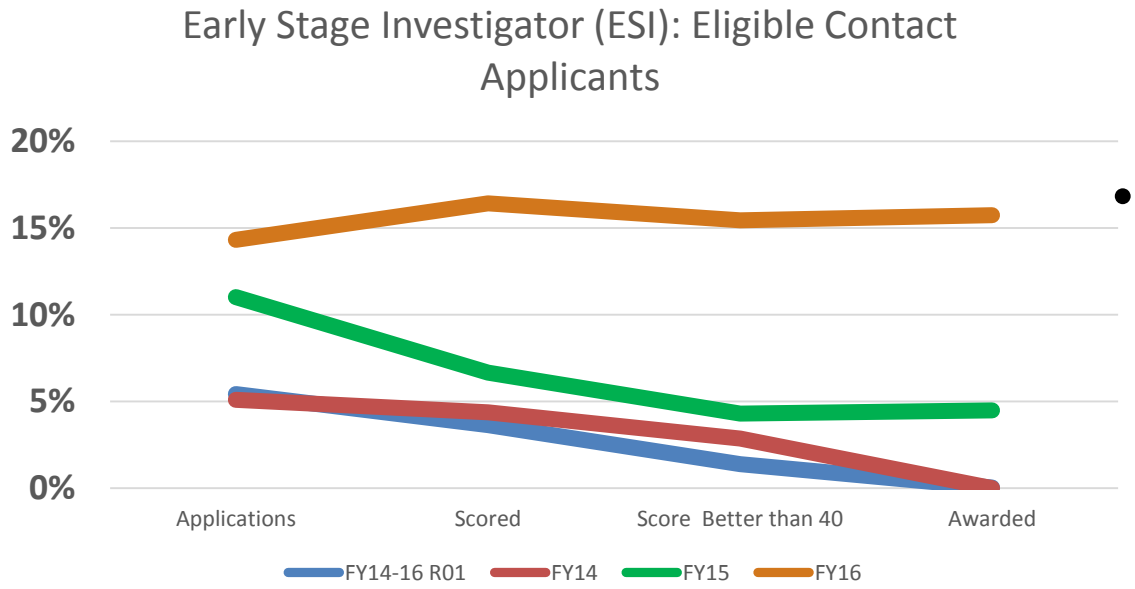


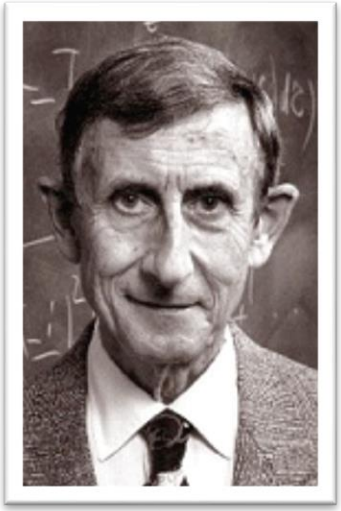


- The BRAIN Initiative is reaching early stage investigators and their applications are doing spectacularly well
- New BRAIN FOAs attract both NI and ESI applicants. Source of the increase in FY 15 and FY16
- The R21 Funding opportunity for large scale recording continues to attract NI and ESI applicants

Control is neuroscience across all ICs.

Where Does Scientific Progress Come From?

"**New directions in science are launched by new tools much more often than by new concepts.** The effect of a concept-driven revolution is to explain old things in new ways. The effect of a tool-driven revolution is to discover new things that have to be explained."



Freeman Dyson (1997) *Imagined Worlds*
Harvard University Press, Cambridge, MA