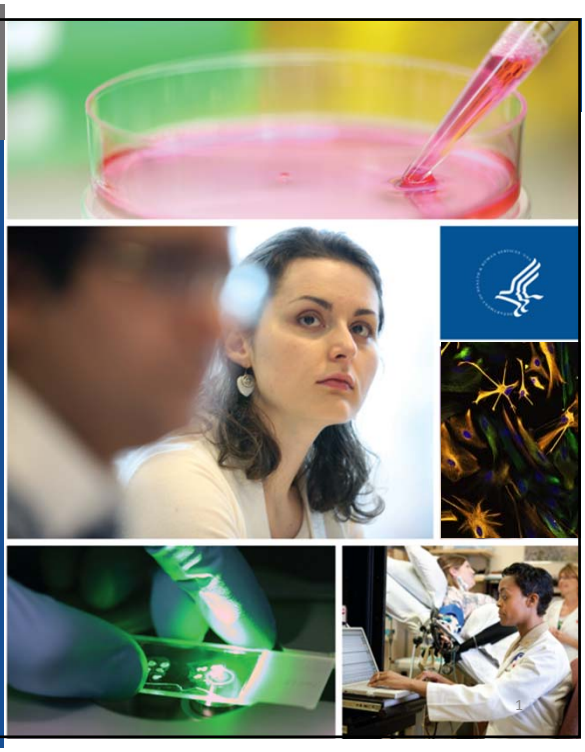
National Institute of Neurological Disorders and Stroke

What is NIH doing for Neurology?

University of Rochester *Goldberg 50th Anniversary Lecture*

September 23, 2016

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



Congratulations University of Rochester Neurology!

- Since its origins in 1966 with six faculty members, the department has grown to include **over 100 faculty members**, 24 adult neurology residents, 6 child neurology residents, 14 fellows, 15 advanced practice providers and over 100 staff members.
- Goldberg Lecture

1966 50 YEARS 2016
UR MEDICINE NEUROLOGY

1850 MELIORA

UNIVERSITY of ROCHESTER

National Institute of Neurological Disorders and Stroke

Investments in Research at University of Rochester

Actively Funded Investments:

- NIH Funding: $197.6 M
- NINDS Funding: $13.3 M

NINDS supports a range of basic and applied research projects, including:

- Parkinson's Disease
- Epilepsy
- Muscular Dystrophy
- Spinal Cord Injury
- Glial Biology
- Ischemic Injury
- Neural Circuits
- Neuroinflammatory Response to HIV
- Blood Brain Barrier

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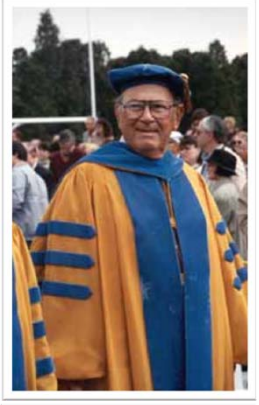
Emanuel and Nathalie Goldberg



- Nathalie Levey Goldberg, Class of 1939
- Emanuel Goldberg, Class of 1932
  - M.S. in Chemistry 1933
  - Developed the first plastic pipet jars
  - Founded Nalge Company (currently Nalgene Nunc) in 1949 in Rochester, New York
  - Trustee of the University of Rochester, Eastman Dental Center until his death in 1999

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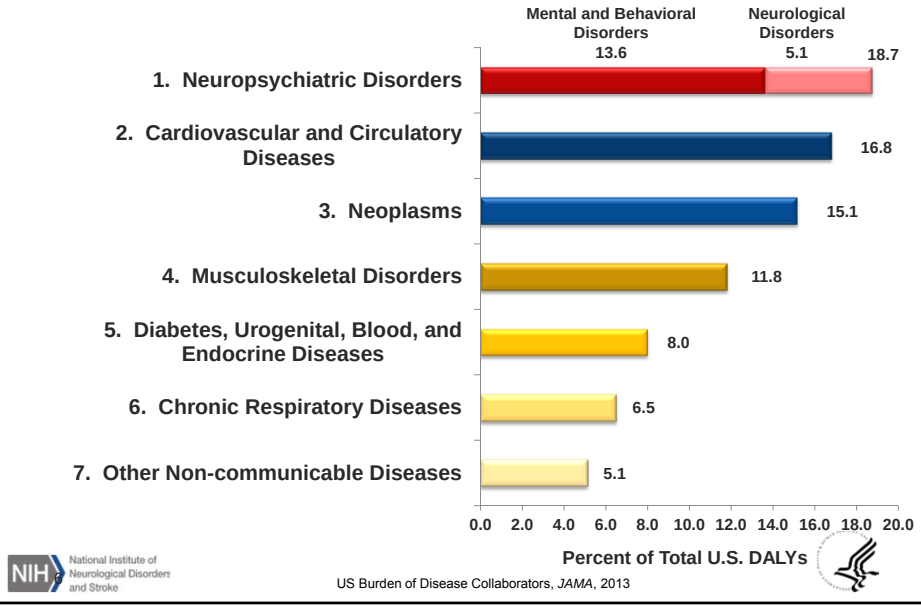
Tough Problems

U.S. Burden of Diseases: 291 Diseases and Injuries

Leading Categories of DALYs 2010



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US Burden of Disease Collaborators, *JAMA*, 2013

The Challenge for the 21st Century

Brain disorders – both neurodevelopmental and neurodegenerative – will be the **most disabling and most costly** of the chronic diseases—they will be in the 21st century what infectious diseases were in the 20th century.

We do NOT know enough about how brain circuits function and how they dysfunction to cause disability for persons with neuro/mental/substance abuse disorders.

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Public Interest in Brain Research is Growing

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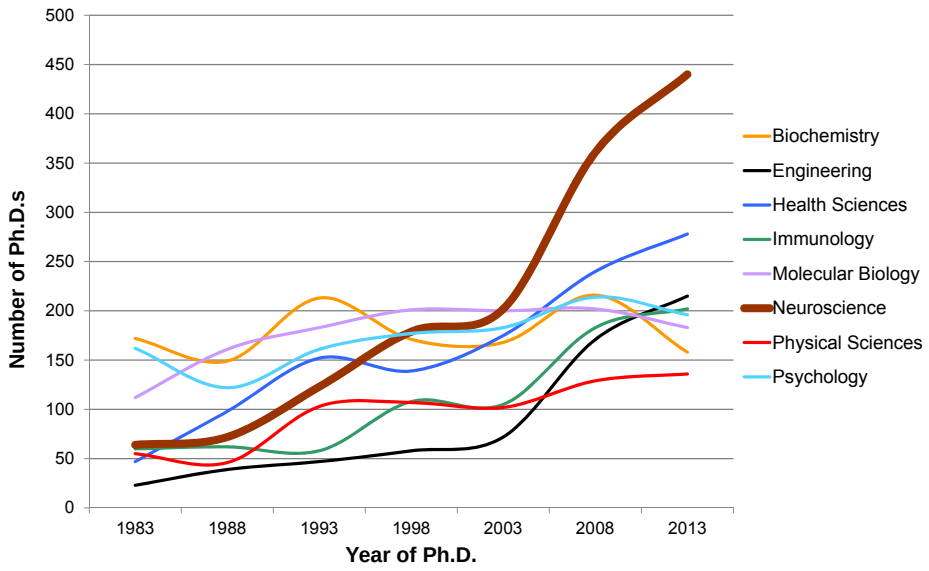
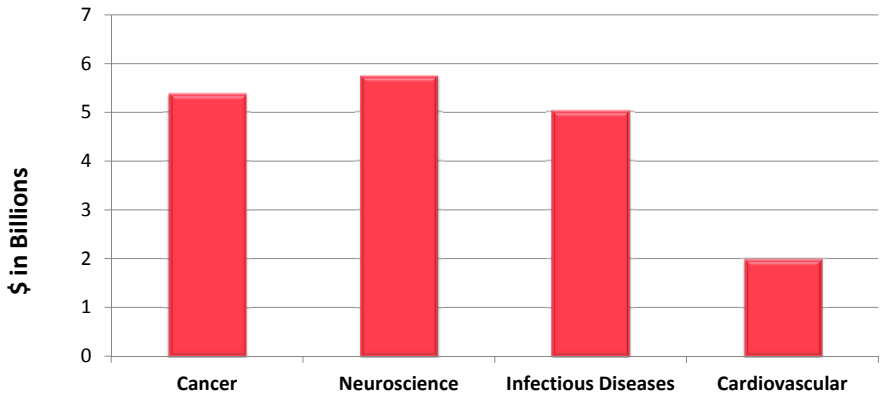
Trends in Fields of Study of Trainees and Fellows Receiving Ph.D.s



2015 NIH Funding of Disease Categories



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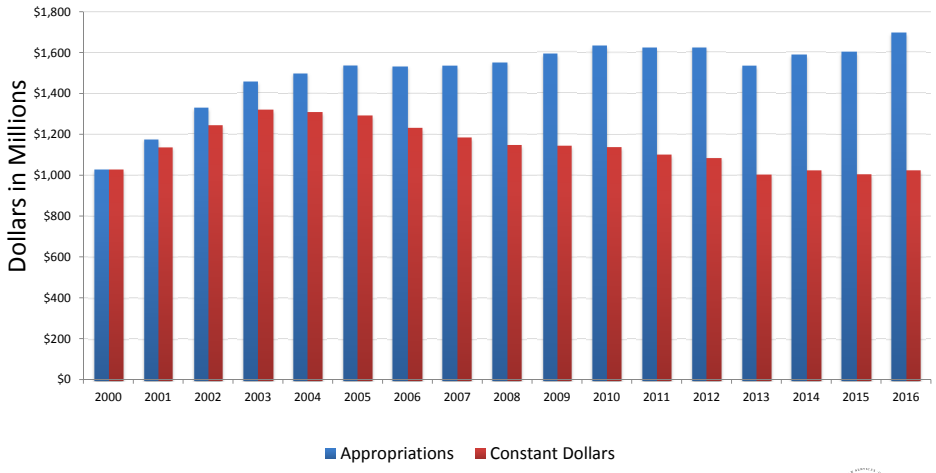
Decline in NINDS Purchasing Power



Adjustment Factor based on Biomedical Pricing Index (BRDPI)

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Senate L-HHS-Ed Appropriations Subcommittee Hearing:

"NIH: Investing in a Healthier Future"

- October 7, 2015
- Witnesses: NIH Director; directors from NINDS, NIGMS, NCI, NIDDK, NIDA
- Chairman Blunt asked witnesses to talk about their research programs and how to increase opportunities and training for young investigators
- Several broad themes emerged
  - What would you do if you had $2-3 billion more money?
  - Ramifications of a Continuing Resolution (e.g. on PMI, BRAIN)
  - Importance of increasing opportunities for young scientists to ensure future discoveries and sustain economic benefits of biomedical research
  - Balance of funding across various diseases at NIH (e.g. HIV)

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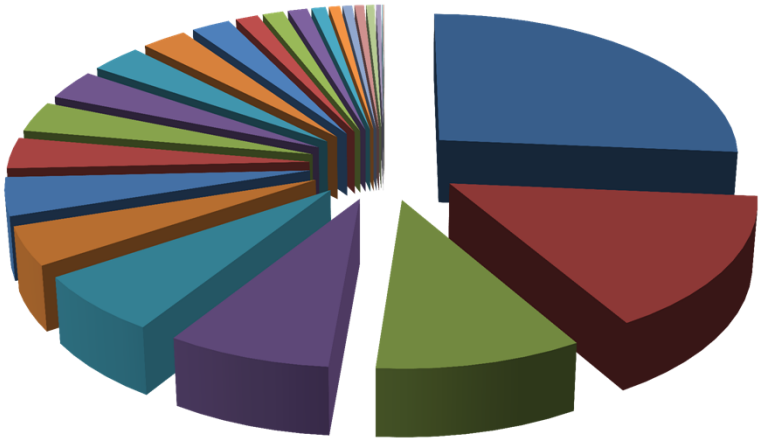
NIH Support for Neuroscience Extends across Many Institutes



RCDC reporting - ($$$ in billions)

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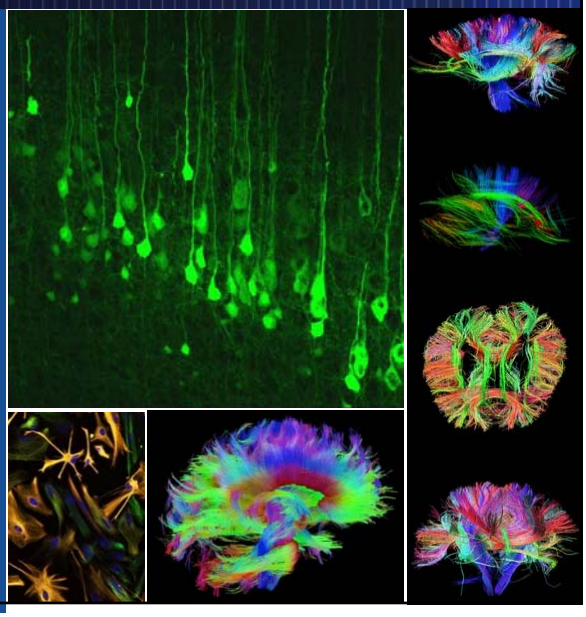
NIH Blueprint for Neuroscience Research

NIH Neuroscience Blueprint:
Multiple ICs Working Together to Advance Neuroscience



Appropriation History
(Dollars in Billions)

	FY 2013	FY2014	FY 2015	FY 2016	FY 2017 PB	FY 2017 House	FY 2017 Senate
NINDS	$1.534	$1.589	$1.605	$1.695	$1.695	$1.751	$1.803
NINDS % Change	-5.6%	3.6%	1.0%	5.6%	0.0%	3.3%	6.4%
NIH	$29.2	$30.2	$30.3	$32.3	$33.1	$33.3	$34.1
NIH % Change	-5.5%	3.4%	0.5%	6.6%*	2.6%	3.1%	5.5%

*minus the BRAIN funds = 3.9% for IC budget

FY2017 President's Budget includes:

- IC budget is unchanged from FY16
- NCI receives Cancer Moonshot $680m
- BRAIN increase of $45m in Office of the Director
- Precision Medicine increase $100m in Office of Director

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Competing RPG Trends

	2010	2011	2012	2013	2014	2015
Competing Awards	699	749	701	702	750	819
Number of Applications	3,097	3,549	3,588	3,551	4,002	4,007
Success Rate	22.6%	21.1%	19.5%	19.8%	18.7%	20.5%
Average Cost	$405K	$392K	$378K	$378K	$396k	$379k
Payline (Percentile)	14	14	15	14	14	14

Data includes complete RPG portfolio of Unsolicited Announcements, RFAs, PAs, PASs
Increase in applications led to increase in outyear commitments
With continuing resolution looming for FY'17 payline reduced to 12%-tile.

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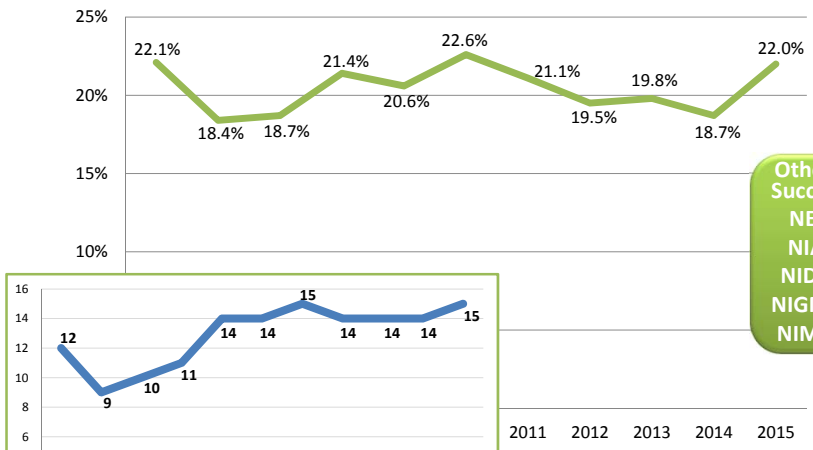
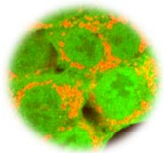
NINDS Success Rate

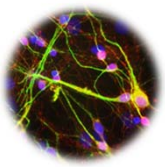


Other IC FY15 Success Rates:
NEI: 23.5%
NIA: 20.9%
NIDA: 22.3%
NIGMS: 29.0%
NIMH: 22.2%

NINDS Supports Research Across the Rare Disease Spectrum

Absence of Septum Pellucidum
Acute Disseminated Encephalomyelitis
Adie Syndrome
Agnosia
Aicardi Syndrome
Aicardi-Goutieres Syndrome
AIDS–Neurological Complications
Alexander Disease
Alpers' Disease
Alternating Hemiplegia
Amyotrophic Lateral Sclerosis (ALS)
Anencephaly
Apraxia
Arachnoid Cysts
Arachnoiditis
Ataxia Telangiectasia
Barth Syndrome
Becker's Myotonia
Behcet's Disease
Bell's Palsy
Binswanger's Disease
Blepharospasm
Brown-Sequard Syndrome
CADASIL
Cerebellar Degeneration
Cerebellar Hypoplasia
Cerebral Cavernous Malformation
Cerebral Palsy
Charcot-Marie-Tooth Disease
Chiari Malformation
Choreoacanthocytosis
Cockayne Syndrome Type II
Coffin-Lowry Syndrome
Complex Regional Pain Syndrome
Corticobasal Degeneration
Cytomegalic Inclusion Body Disease
Dancing Eyes-Dancing Feet Syndrome
Dandy-Walker Syndrome
Dravet Syndrome
Dystonias
Early Infantile Epileptic Encephalopathy
Empty Sella Syndrome
Encephalitis Lethargica
Essential Tremor
Fabry Disease
Familial Dysautonomia
Farber's Disease
Friedreich's Ataxia
Frontotemporal Dementia
Gaucher Disease
Gerstmann's Syndrome
Gerstmann-Straussler-Scheinker Disease
Giant Axonal Neuropathy
Glycogen Storage Disease
Guillain-Barre Syndrome
HTLV-1 Associated Myelopathy
Huntington's Disease
Hydranencephaly
Inclusion Body Myositis
Joubert Syndrome
Kearns-Sayre Syndrome
Kennedy's Disease
Kuru
Landau-Kleffner Syndrome
Lennox-Gastaut Syndrome
Leukodystrophy
Locked-in Syndrome
Lyme Disease-Neurological Complications
Menkes Disease
Meralgia Paresthetica
Microcephaly
Miller-Fisher Syndrome
Moebius Syndrome
Myasthenia Gravis
Narcolepsy
Neuroleptic Malignant Syndrome
Niemann-Pick Disease
Normal Pressure Hydrocephalus
Olivopontocerebellar Atrophy
Pantothenate Kinase-Associated Neurodegeneration
Paroxysmal Hemicrania
Pick's Disease
Post-Polio Syndrome
Primary Lateral Sclerosis
Progressive Hemifacial Atrophy
Pseudotumor Cerebri
Rasmussen's Encephalitis
Refsum Disease
Rett Syndrome
Sandhoff Disease
Semantic Dementia
Septo-Optic Dysplasia
Spinal Muscular Atrophy
Stiff Person Syndrome
Sturge-Weber Syndrome
Subacute Sclerosing Panencephalitis
Tay-Sachs Disease
Thoracic Outlet Syndrome
Tourette Syndrome
Trigeminal Neuralgia
Transverse Myelitis
Tuberous Sclerosis
Von-Hippel-Lindau Disease
Wernicke-Korsakoff Syndrome
West Syndrome
William's Syndrome
Wilson Disease
Wolman's Disease
Zellweger Syndrome





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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

http://www.ninds.nih.gov/about_ninds/plans/NINDS_strategic_plan.htm

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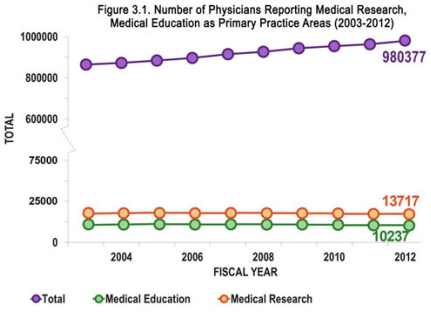
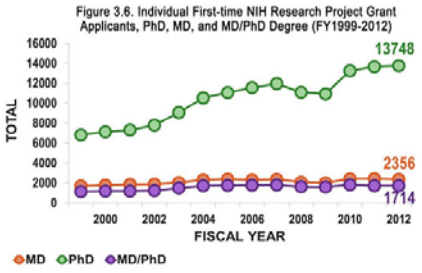
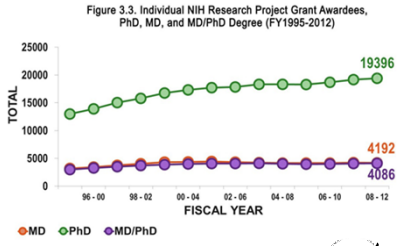
Number of Physicians in Research Careers Remains Flat







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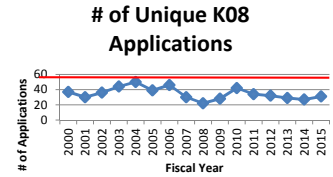
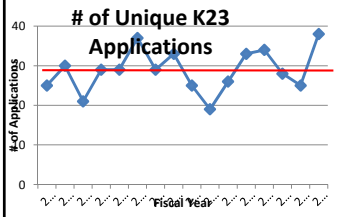
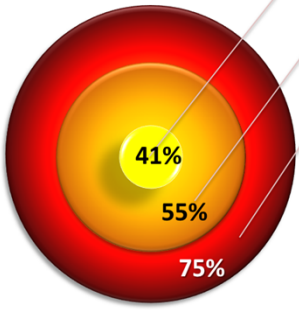
NINDS Clinician K-to-R Transition







All K08s/K23s that got R01s

All K08s/K23s that applied and got R01s

All K08s/K23s that have independent funding

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Data Source: K awards terminating 2003-11

NINDS Office of Training and Workforce Diversity
Bridging the Gaps

MD/PhD Fellowships

MD and MD/PhD

R25

Resident/ Fellow

K12/K08/K23/K99

Faculty

K02

R01

Independent Investigator

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Key Policy Issues

Reproducibility of Research Results

- NIH to stress the **importance of experimental rigor and transparency of reporting research findings** to enhance ability of others to replicate them.
- We think that needs to be shift from emphasis on "statistical significant P-value" to "effect size".

Early Investigators

- NINDS to provide 10 percentile point advantage to early stage new investigators.
- NIH is directed to develop a new approach with actionable steps to **reduce the average age at which an investigator first obtains R01 funding**.

Basic Biomedical Research – urges **continued focus on basic biomedical research**.

Burden of Disease – urges NIH to consider burden for research investments. **NIH must include the number of Americans affected by each category listed in the RCDC database**.

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The Growing Challenge

- Noted by research community; in multiple publications
  - Across research areas
  - Especially in preclinical research

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Enhancing Reproducibility through Rigor and Transparency

- ✓ *Guidance crafters*
- ✓ *Journal editors*
- ✓ *Reviewers*
- ✓ *End users*

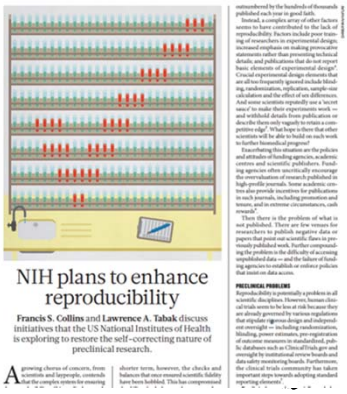
A call for transparent reporting to optimize the predictive value of preclinical research

Nature 2012; 490: 187-191

Story C. Landis[1], Susan G. Amara[2], Khusru Asadullah[3], Chris P. Austin[4], Robi Blumenstein[5], Eileen W. Bradley[6], Ronald G. Crystal[7], Robert B. Darnell[8], Robert J. Ferrante[9], Howard Fillit[10], Robert Finkelstein[1], Marc Fisher[11], Howard E. Gendelman[12], Robert Golub[13], John L. Goudreau[14], Robert A. Gross[15], Amelie K. Gubitz[1], Sharon E. Hesterlee[16], David W. Howells[17], John Huguenard[18], Katrina Kelner[19], Walter Koroshetz[1], Dimitri Krainc[20], Stanley E. Lazic[21], Michael S. Levine[22], Malcolm Macleod[23], John M. McCall[24], Richard T. Moxley III[25], Kalyani Narasimhan[26], Linda J. Noble[27], Steve Perrin[28], John D. Porter[1], Oswald Steward[29], Ellis Unger[30], Ursula Utz[1] & Shai D. Silberberg[1]

A Preclinical Consortium Approach for Assessing the Efficacy of Combined Anti-CD3 Plus IL-1 Blockade in Reversing New-Onset Autoimmune Diabetes in NOD Mice

Ronald G. Gill[1*], Philippe P. Pagni[2*], Tinalyn Kufper[1], Clive H. Wasserfall[3], Songyan Deng[4], Amanda Posgai[3], Yulia Manenkova[2], Amira Bel Hani[2], Laura Straub[5], Philip Bernstein[6], Mark A. Atkinson[3*], Kevan C. Herold[4*], Matthias von Herrath[2*], Teodora Staeva[7], Mario R. Ehlers[5] and Gerald T. Nepom[8]



NIH plans to enhance reproducibility

Francis S. Collins and **Lawrence A. Tabak** discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring shorter term, however, the checks and balances that once ensured scientific fidelity have been hobbled. This has compromised

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NINDS Is Investing Across the Research Spectrum

Basic Research	Disease-focused research	Target ID	Assay Dev.	High Thru-put Screen	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

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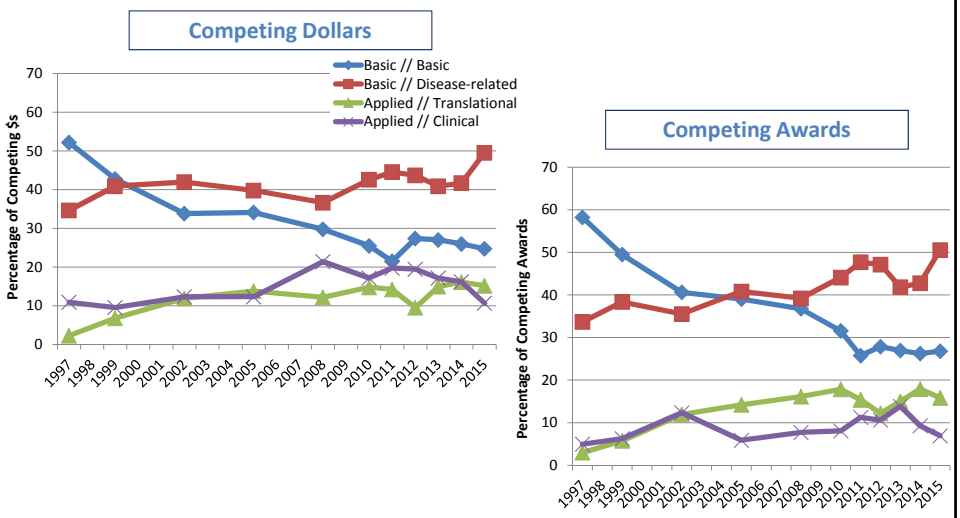
NINDS Funding Trends



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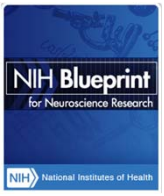
NINDS Office of Translational Research



- Goal – advance promising therapies to hand off to biotech/pharma companies
  - 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 (BPN) for small molecules
    - Development of small molecules
    - Provides investigators with access to consultants and contracts that provide discovery, preclinical development, and clinical trial support
  - Cooperative Research to Enable and Advance Translational Enterprises (CREATE) Bio and Devices
    - 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

http://www.ninds.nih.gov/funding/areas/translational_research/

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NeuroNEXT : Network for Excellence in Neuroscience Clinical Trials

The NeuroNEXT program aims to:

- Provide a robust, standardized, and accessible infrastructure to conduct studies of treatments for neurological diseases
- Create and leverage partnerships with academia, private foundations, and industry
- Increase the efficiency of clinical trials
- Support scientifically sound, possibly biomarker-informed, exploratory clinical trials that provide data for clear go/no-go decisions
- Expand the pool of experienced clinical investigators and research staff

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NINDS Funding Opportunity Announcement

Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases (U01) PAR-16-020

- Purpose: to support clinical studies that will fill gaps in the design of upcoming clinical trials in rare neurological and neuromuscular diseases by validating clinical outcome measures or biomarkers, or by characterizing cohorts of relevant patients.
- Appropriate trial readiness projects can be “stand alone” studies, or they can be ancillary to other, ongoing clinical studies.
- Higher priority will be given to diseases/conditions that currently or soon will have multiple candidate therapeutics or devices ready for testing in clinical trials, but that lack critical components of trial readiness that are needed for moving forward.
- NINDS expects this will accelerate the initiation of clinical trials for rare diseases and increase the likelihood of success in those trials.
- Upcoming application due dates: Feb 17, 2017; Aug 17, 2017; Feb 15, 2018 and Aug 17, 2018
- Expiration date: Aug 18, 2018

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Find out more: http://grants.nih.gov/grants/guide/pa-files/PAR-16-020.html

Parkinson's Disease Biomarker's Program (PDBP)

PDBP Parkinson's Disease Biomarkers Program

Original PDBP Goals (2012)

- Support hypothesis-driven, biomarkers discovery research
  - 15 individual projects funded via original and subsequent funding announcements
- Support the collection of Clinical Data and Biospecimens
  - 955 Cases, 534 controls

PDBP Annual Meeting: Areas for focus

- Replication, and negative results tracking
- Harmonization/standardization *(esp. imaging)*
- Longitudinal follow-up *(wearables? telephone survey?)*
- Specific cohorts for discovery *(e.g. parkinsonisms, genetic, de novo)*

Future PDBP Goals

- Continue PD biomarkers discovery
- Replicate PD biomarkers
- Differentiate parkinsonian dementias
- Differentiate PD from parkinsonisms (PSP, CBD,MSA, ET)
- Initiate studies of specific cohorts (genetic, diversity)
- Integrate wearables

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The Accelerated Medicines Partnership (AMP) Framework

Accelerate target validation…

- Defined as the accumulation of evidence that a disease intervention point, "th target", will be an effective point for therapeutic interaction

… with a specific focus on disease deconstruction…

- Defined as the systematic characterization of heterogeneous, poorly understoo diseases in human populations, combining clinical and molecular information i order to facilitate rational selection of targets, identification of patients, subpopulations for trials and customized prophylaxis, diagnosis and treatment decisions

… through a collaborative, public-private partnership

- Focusing on "pre-competitive" target validation activities that would not be efficiently done without collective action
- Working collaboratively across government, academia and industry through harmonized efforts that harness collective capabilities & scale
- Initial design led to successful programs in three disease areas (Alzheimer's disease, Type II diabetes, RA & related disorders)
- A new concept was submitted for Parkinson's Disease and design is being developed

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NIH Neurobiobank: Goals

- To increase the availability of human disease and control brains and related biospecimens by increasing public awareness of the value of tissue donation for understanding brain disorders.
- To facilitate the distribution of high-quality, well-characterized human-post mortem brain tissue for the research community.
- To make available to the research community, a centralized resource of Standard Operating Procedures (SOPs) and protocols used by our networked sites in the acquisition, preparation, and distribution of tissue.

- **Mount Sinai NIH Brain and Tissue Repository. James J Peters VA Medical Center**
- **The Human Brain and Spinal Fluid Resource Center UCLA**
- **University of Miami Brain Endowment Bank**
- **Brain Tissue Donation Program at the University of Pittsburgh**
- **University of Maryland Brain and Tissue Bank**

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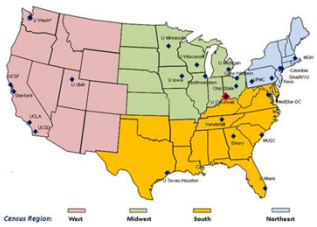
NIH Stroke Network

National and Regional Coordinating Centers



NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
Funded by a Grant from the National Institutes of Health

- Coordinating Center- U of Cincinnati
  - 1 IRB, 1 master contract agreement
- Data Management Center- Medical University of South Carolina
- Coordinated study execution and funding with Canadian Institute of Health Research's stroke sites
- Principal Investigator/Statistician - open to all
- 25 clinical hubs, >200 hospitals
- $50k/year/hub for training
- Infrastructure Total Cost- ~$11million/year

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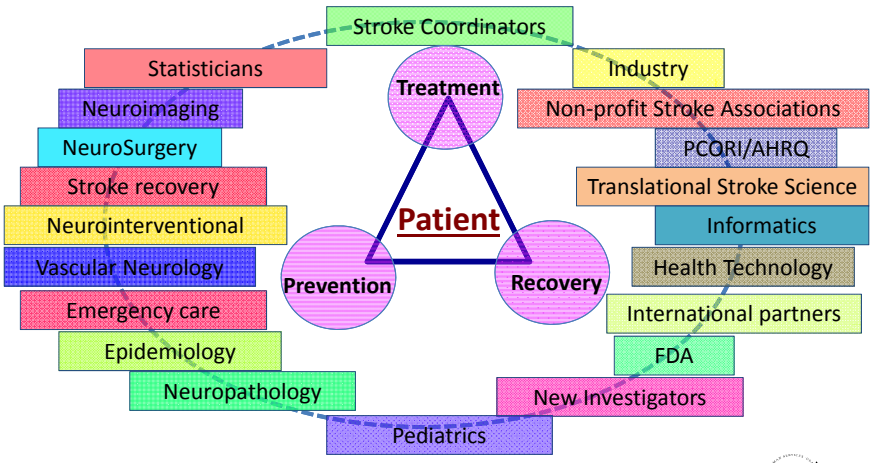
StrokeNet

Teamwork is the Solution



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Network for Emergency Care Trials

- Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN).
  - Will conduct high-quality, multi-site clinical trials to improve the outcomes for patients with neurologic, cardiac, respiratory, and hematologic, and trauma emergency events
  - SIREN will harness multidisciplinary emergency care expertise to provide scientific leadership and the infrastructure required to conduct large, simple, pragmatic clinical trials to advance knowledge of optimal patient management in the pre-hospital and ED setting
- An NINDS and NHLBI initiative in coordination with Dept. of Defense USAMRC.

NIH National Institute of Neurological Disorders and Stroke

Recent Advances

The NEW ENGLAND JOURNAL of MEDICINE

Walter J. Koroshetz
@NINDSdirector
Follow

Randomized Trial of Thymectomy in #MyastheniaGravis shows benefit of surgery. Thanks to the patients & investigators

Randomized Trial of Thymectomy in Myasthenia Gravis —...
Original Article from The New England Journal of Medicine — Randomized Trial of Thymectomy in Myasthenia Gravis
nejm.org

RETWEETS 5 LIKES 2

http://www.nejm.org/doi/pdf/10.1056/NEJMoa1602489

nature COMMUNICATIONS

ARTICLE

Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis

http://www.nature.com/articles/ncomms11934

IONIS PHARMACEUTICALS
Biogen

Biogen and Ionis Pharmaceuticals Report Nusinersen Meets Primary Endpoint at Interim Analysis of Phase 3 ENDEAR Study in Infantile-Onset Spinal Muscular Atrophy

http://media.biogen.com/press-release/neurodegenerative-diseases/biogens-investigational-alzheimers-disease-treatment-aducan

NIH National Institute of Neurological Disorders and Stroke

Update on Concussion Research

Two neuropath studies ongoing

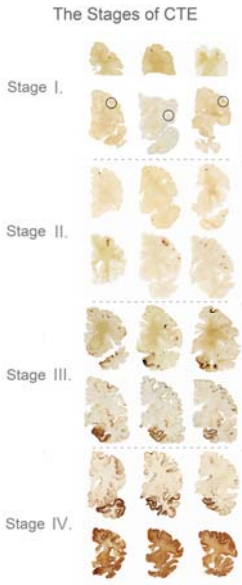
- Published guidelines for pathologic diagnosis of CTE
- Screen of May neuro brain bank for CTE
  - Found in 30% of those with some history of playing contact sports. 0% in matched non-sports cohort and 0% in female cohort.
- Screen of Queen's Square neuro bio bank
  - CTE in 12% and history of TBI in 94%, but TBI not sports related, question raised whether TBI related to falls from neuro conditions.
  - NINDS funded longitudinal study to characterize clinical syndrome of CTE from its appropriated budget.

NINDS-funded longitudinal study to characterize clinical syndrome of CTE from its appropriated budget

NINDS will form a working group of Council to discuss next highest priority opportunities in concussion research

- In concert with NICHD
- Jonathan Mink to lead

- Will hold a workshop and create research plan
- Concept clearance for Council
- Discuss research plan with FNIH



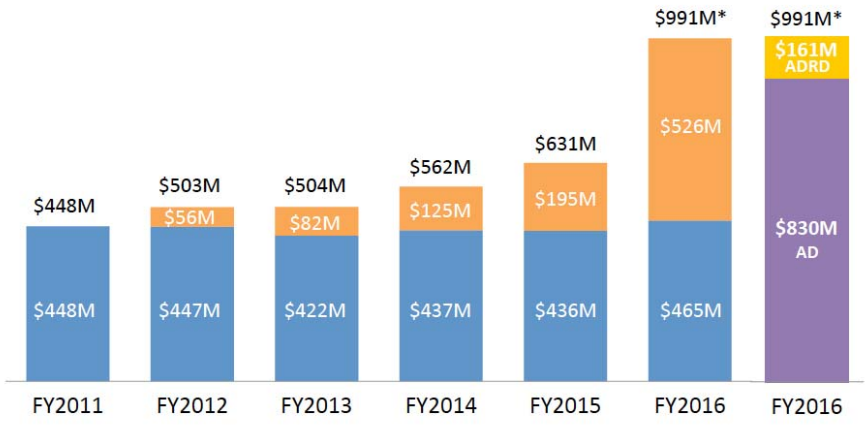
ALZHEIMER'S DISEASE-RELATED DEMENTIAS SUMMIT 2016 | MARCH 29-30 2016

US National Alzheimer's Plan
Goals

1. Prevent and effectively treat AD by 2025
2. Enhance care quality and efficiency
3. Expand supports for people with AD and families
4. Enhance public awareness/engagement
5. Improve data to track progress

ALZHEIMER'S DISEASE-RELATED DEMENTIAS SUMMIT 2016 | MARCH 29-30 2016

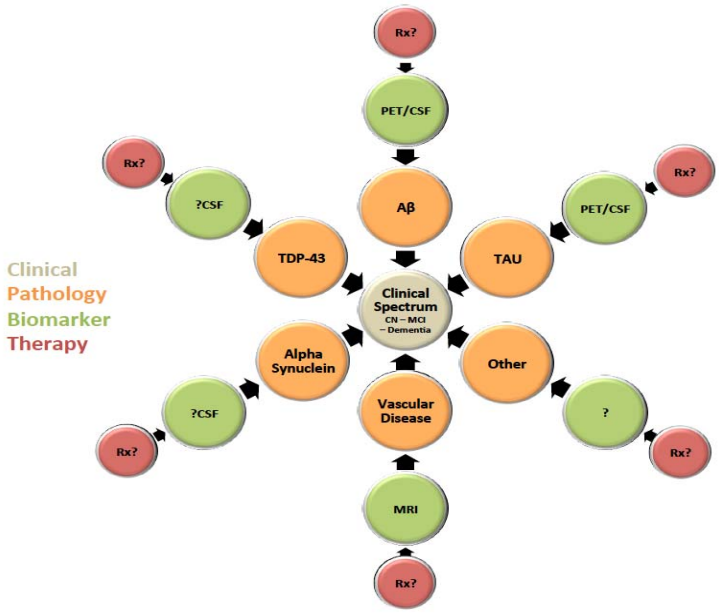
AD/ADRD Research Increases at NIH



*Projected

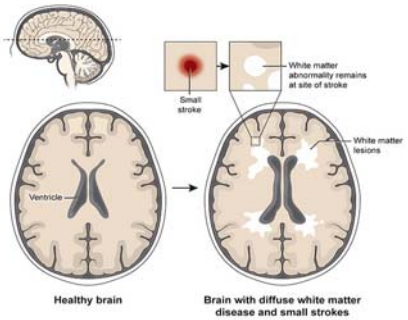
Courtesy of Robert Egge

Dementia results from a spectrum of pathobiologies

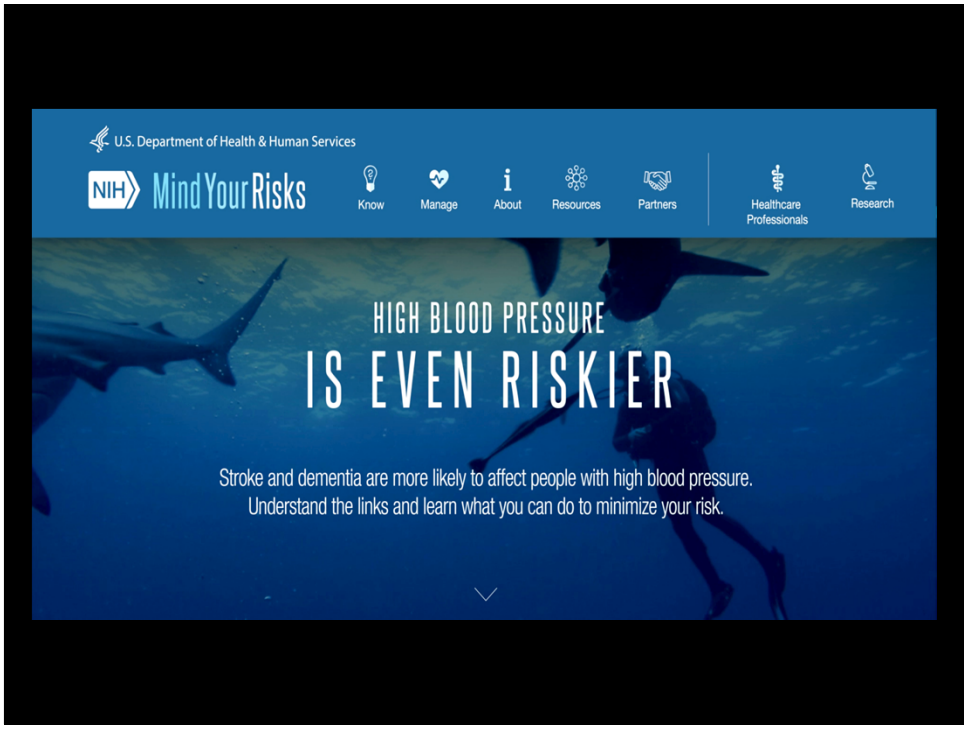


Most **Strokes Are Silent:** **Consequences are Cognitive Impairment and Dementia**

- **Infarction**
  - Usually small and multiple seen on MRI or at autopsy
  - Associated with cognitive impairment and dementia
- **Micro hemorrhages**
  - Hypertensive - deep
  - Amyloid angiopathy - cortically located associated with Alzheimer's Disease in half.

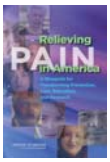


42



National Pain Strategy:
A Comprehensive Population Health Level Strategy for Pain

2010 Patient Protection & Affordable Care Act

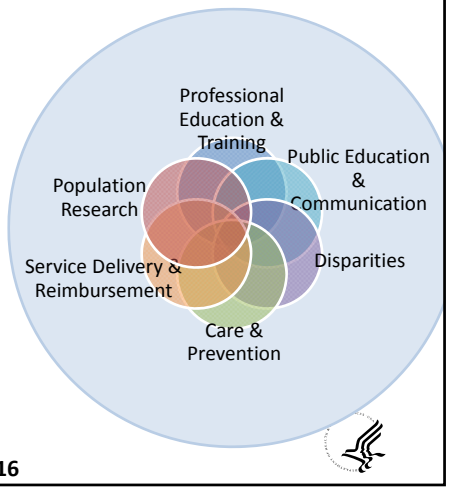


INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

2011: *Relieving Pain in America*

NIH The Interagency Pain Research Coordinating Committee

2012 Assistant Secretary for Health, HHS tasked IPRCC and NIH to address IOM Recommendation: "*develop a comprehensive, population health-level strategy for pain prevention, treatment, management, education, reimbursement, and research that includes specific goals, actions, time frames, and resources.*"



NIH National Institute of Neurological Disorders and Stroke

Released March 2016

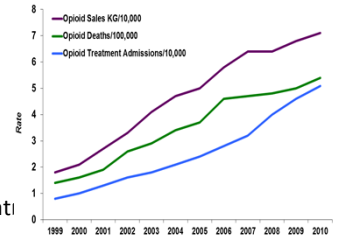
National Institutes of Health

Pathways to Prevention: NIH OFFICE of DISEASE PREVENTION September 29–30, 2014

The Role of Opioids in the Treatment of Chronic Pain

Consensus Workshop to review:

- Long-term effectiveness of opioids for chronic pain.
- Risks of opioids for various populations.
- Outcomes of opioid based pain care on function, addiction, & abuse.
- Effectiveness of risk mitigation strategies for opioid treat
- Optimal pain management with opioids.



Follow-up Partners Meeting: Priority Research Recommendations:

- Identify pain conditions & patient populations most likely to benefit and incur harm from opioids.
- Develop and evaluate multidisciplinary pain interventions.
- Develop and validate research measurement tools for identification of risk and outcomes related to long-term opioid use, which can be adapted for clinical settings.

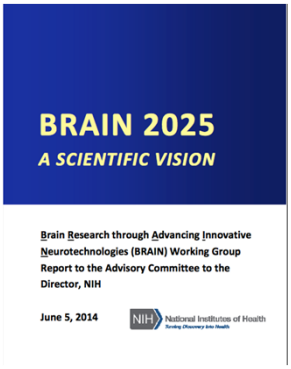
National Institute of Neurological Disorders and Stroke

Chronic Fatigue Syndrome

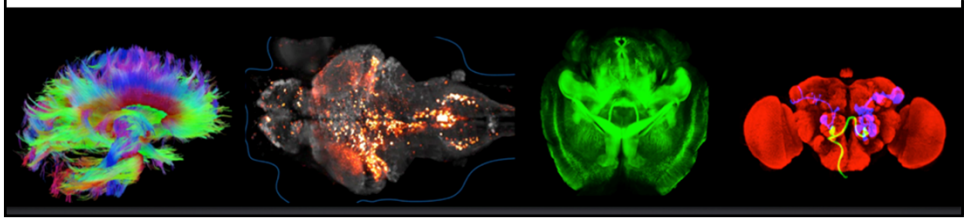
- Affects between 800,000 - 2.5 million in the US
- 75% affected are women
- Cause unknown but many have distinct onset with flu-like symptoms
- <u>Plans for CFS/Myalgic Encephalitis Research</u>
  - NIH-wide intramural protocol through IRB to begin phenotyping, neuro and immunologic studies
    - Led by Dr. Avi Nath
  - Trans-NIH working group developing an extramural research program
    - Led by Dr. Vicky Whittemore

National Institute of Neurological Disorders and Stroke

The BRAIN Initiative®



- A focus on circuits and networks
- Measure the fluctuating electrical and chemical patterns within circuits
- Understand how all of this helps generate our unique thoughts and actions



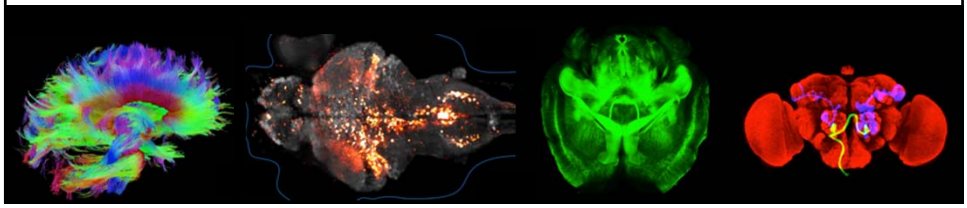
What's the problem? It's the circuits stupid!

We need to be able to see the circuits in action to:

- Understand how the brain moves, plans, executes
- Understand how to monitor and manipulate circuits for improved function.
- The disability that patients with neuro/mental/substance abuse disorders suffer is a direct result of disordered brain circuits.

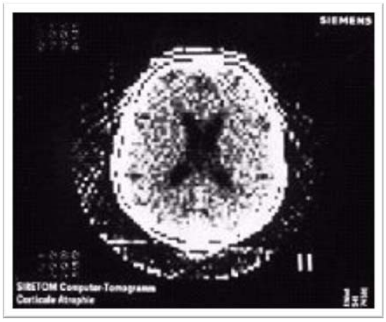
Molecular/Structural Pathology → Circuit Dysfunction → Neuro/Mental Functional Disability

- Goal: Make circuit normalization/compensation the target of intervention: Pharmacologic/Cell/Device/PT,OT, Speech Therapy



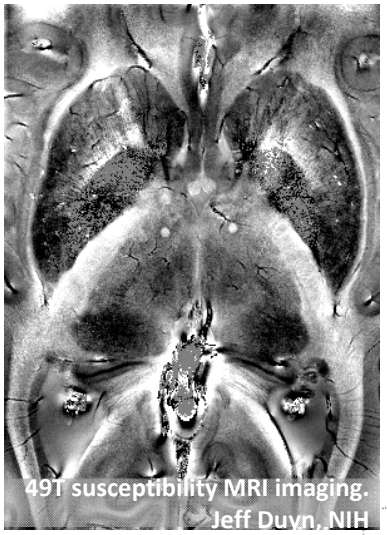
What Is Next?

1974



Original axial CT image form Siretom CT scanner circa 1975. Physicians were fascinated by the ability to see the brain and ventricles for the first time.

2016



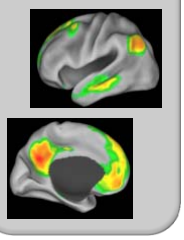
49T susceptibility MRI imaging.
Jeff Duyn, NIH

NIH National Institute of Neurological Disorders and Stroke

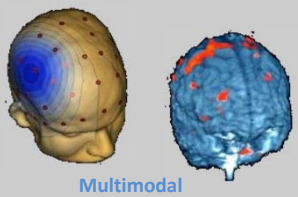
NIH Human Connectome Project
Mapping the Human Connectome

Structural Connectivity

Functional Connectivity

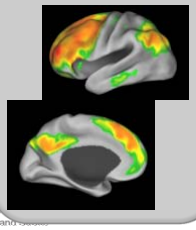


Temporal Connectivity

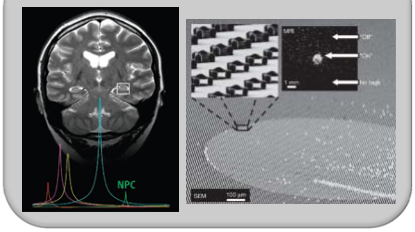


Multimodal Integration

Molecular Imaging



New Molecular Imaging



Wash U
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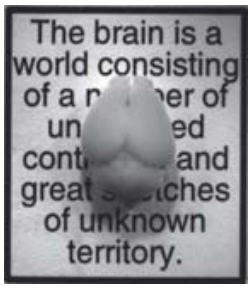
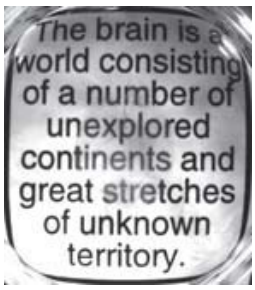
MGH

NIH

CLARITY: *Neuroanatomy for the 21st Century*

Deisseroth et al, Stanford

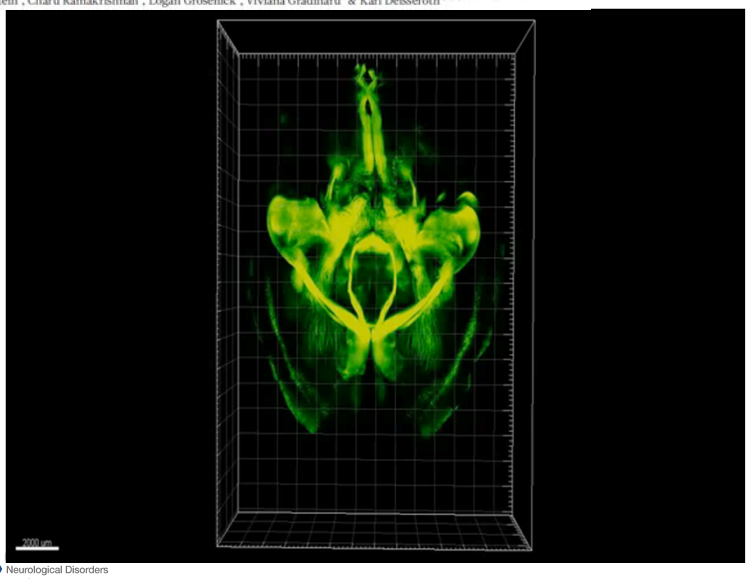




NIH National Institute of Neurological Disorders and Stroke

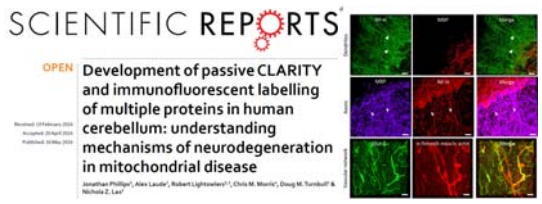
Structural and molecular interrogation of intact biological systems

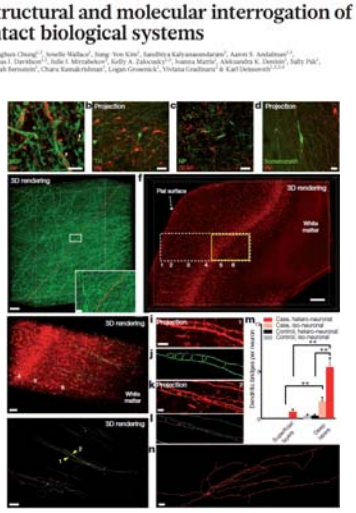
Kwanghun Chung[1-3], Jenelle Wallace[1], Sung-Yon Kim[1], Sandhiya Kalyanasundaram[2], Aaron S. Andalman[1-2], Thomas J. Davidson[1,2], Julie J. Mirzabekov[1], Kelly A. Zalocusky[1,2], Joanna Mattis[1], Aleksandra K. Denisin[1], Sally Pak[1], Hannah Bernstein[1], Charu Ramakrishnan[1], Logan Grosenick[1], Viviana Gradinaru[2] & Karl Deisseroth[1-2,3,4]



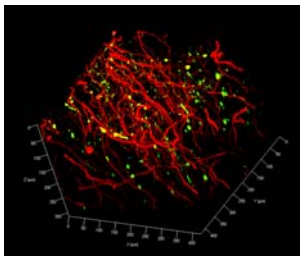
NIH Neurological Disorders and Stroke

Bringing CLARITY to the Human Brain





Neuropathology and Applied Neurobiology Bringing CLARITY to the human brain: visualization of Lewy pathology in three dimensions Liu AK, Hurry ME, Ng OT, DeFelice J, Lai HM, Pearce RK, Wong GT, Chang RC, Gentleman SM.
Z-stack image of double immunofluorescence with anti-αSN (green) and anti-TH (red) antibodies on human midbrain block (z-stack step size 1.5 μm).



Neuropathology and Applied Neurobiology
7 DEC 2015 DOI: 10.1111/nan.12293

Seven High Priority Research Areas

Brain Cell Types

1. **Discovering diversity:** Identify and provide experimental access to the different brain cell types to determine their roles in health and disease.

Tools for Circuit Diagrams

2. **Maps at multiple scales:** Generate circuit diagrams that vary in resolution from synapses to the whole brain.

Tech. to Monitor Neural Activity

3. **The brain in action:** Produce a dynamic picture of the functioning brain by developing and applying improved methods for large-scale monitoring of neural activity.

Precise Inter-ventional Tools

4. **Demonstrating causality:** Link brain activity to behavior with precise interventional tools that change neural circuit dynamics.

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Seven High Priority Research Areas

Theory and Data Analysis Tools

5. **Identifying fundamental principles:** Produce conceptual foundations for understanding the biological basis of mental processes through development of new theoretical and data analysis tools.

Advance Human Neuro-science

6. **Advancing human neuroscience:** Develop innovative technologies to understand the human brain and treat its disorders; create and support integrated human brain research networks.

Integrate Approaches

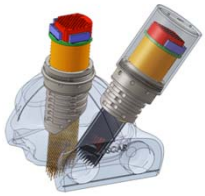
7. **From BRAIN Initiative to the brain**: Integrate new technological and conceptual approaches produced in goals #1-6 to discover how dynamic patterns of neural activity are transformed into cognition, emotion, perception, and action in health and disease.

NIH National Institute of Neurological Disorders and Stroke

THE BRAIN INITIATIVE®

Electrode Development

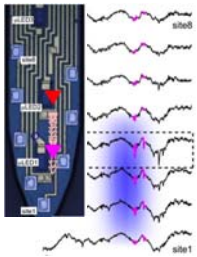
Higher density, less invasive, longer lasting, optogenetic stimulation, transmitter measurements



Dual 96 channel electrode microdrives targeting vmPFC and anterior Insula in NHP
-- *Graymatter Research Inc.*

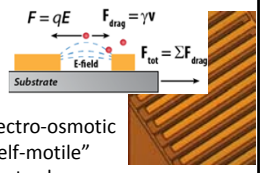
Diamond electrode for stable and calibrated transmitter measurement -- *Mayo Clinic*

Integrated micro-LEDs for selective optogenetic control
-- *U. Michigan*



Flexible polymer probe - long-lasting, high-density recordings
-- *Lawrence Livermore National Labs*

CMOS multi-electrode array with >500 contacts
-- *Italian Institute of Technology*



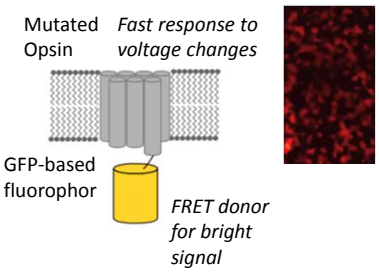
Electro-osmotic "self-motile" electrodes
- *Stanford U.*

THE BRAIN INITIATIVE®

Probe Development

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

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



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

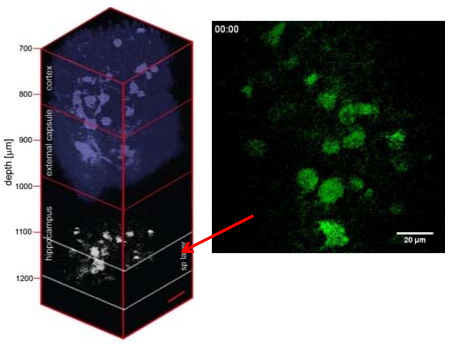
GFP Linked bacterial protein mutated to bind serotonin

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

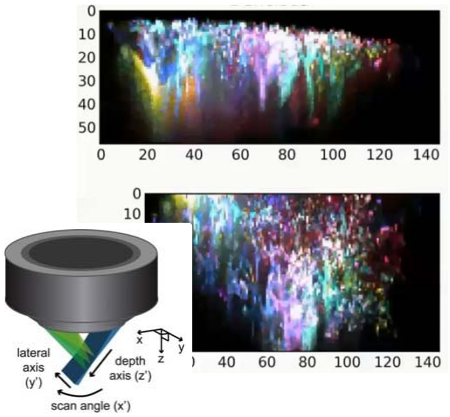
THE BRAIN INITIATIVE®

Optical Instrumentation

Deeper – anywhere in the brain
Faster – whole volumes rather than single image plane
More precise targeting



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

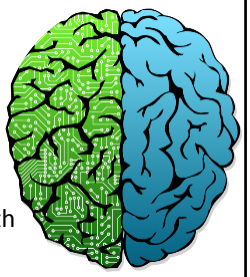


SCAPE imaging of cortical neurons colored by deconvolution – *Columbia (Hillman, Paninski)*

THE BRAIN INITIATIVE®

BRAIN Neuroethics

BRAIN Neuroethics Workgroup



- A consultative ethics group to work with BRAIN leadership and BRAIN investigators
  - Co-chaired by Dr. Christine Grady and Hank Greely
- First meeting was on Feb 9, 2016 with BRAIN PIs conducting invasive human studies
- Second meeting was Aug 3
  - Considered workshops on privacy, ethics of research with invasive neurotechnologies
  - Discussion topics: data sharing; long-term obligations to patients with invasive neural devices
- **R**equest **f**or **I**nformation (RFI): Guidance for Opportunities in Neuroethics closed July 29
- New funding opportunity planned for FY 2017, informed by RFI input

NIH National Institutes of Health
Turning Discovery Into Health

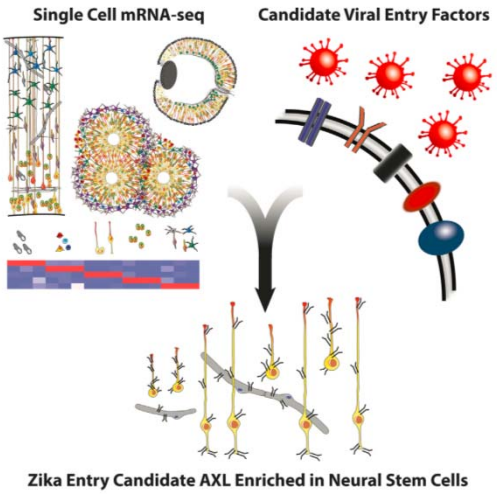
THE BRAIN INITIATIVE®

Exciting New Discoveries

Dr. Arnold Kriegstein and colleagues identify candidate entry receptor for Zika virus in neural stem cells

Single cell RNA-seq analysis of different cell types during early development (*Cell Stem Cell*)

- Examined expression of several candidate entry receptors for Zika virus
- Candidate AXL is highly expressed in several cell types, including human radial glial cells
  - Loss of radial glia founder populations leads to microcephaly
  - AXL expression pattern is conserved in mice, ferrets, and human iPSCs – models for infectivity and developmental effects of Zika virus



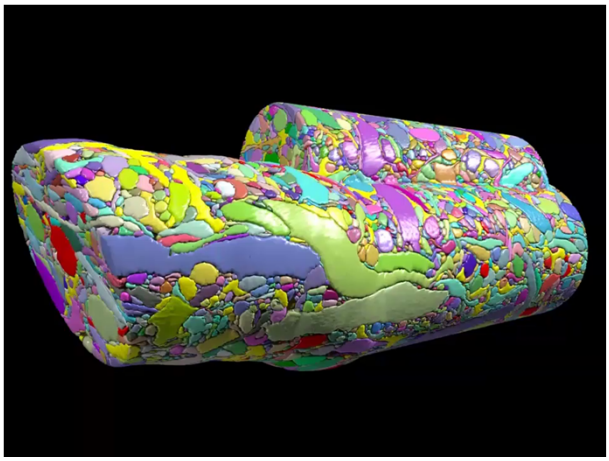
NIH National Institutes of Health
Turning Discovery Into Health

THE BRAIN INITIATIVE®

Exciting New Discoveries

3D Neural Reconstruction

- PI: Jeff Lichtman, PhD and colleagues, *Cell*
- Automated serial sectioning of mouse cortex
- Imaging with a scanning electron microscope
- Virtual, 3D reconstruction and analysis
- Nanometer scale

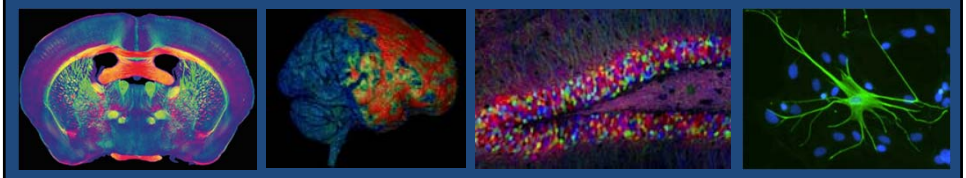


NIH National Institutes of Health
Turning Discovery Into Health

http://braininitiative.nih.gov/

NINDS

Seeking Knowledge about the Brain . . .
Reducing the Burden of Disease



The Precision Medicine Initiative® Cohort Program

- The Program will start by collecting a limited set of standardized data
  - Participant questionnaires
  - Electronic health records
  - A baseline physical evaluation
  - Biospecimens (blood and urine samples)
  - Mobile/wearable technologies
  - Geospatial/environmental data

- Scientific Opportunities
  - Develop quantitative **estimates of risk** for a range of diseases by integrating environmental exposures and genetic factors
  - Identify the causes of individual variation in response to commonly used therapeutics = **pharmacogenomics**
  - Discover **biological markers** that signal increased or decreased risk of developing common diseases
  - Develop **solutions to health disparities**
  - Use **mobile health technologies** to correlate activity, physiological measures, and environmental exposures with health outcomes
  - **Empower study participants** with data and information to improve their own health
  - Create a platform to enable **trials of targeted therapies**

NIH National Institute of Neurological Disorders and Stroke

Approach to Assembling the PMI Cohort

- **One million or more** U.S. volunteers
  - Broadly reflect the diversity of America (including family members of all ages, health statuses, geographic areas, etc.)
  - Strong focus on underrepresented groups
- **Longitudinal cohort**, with continuing interactions, recontact for secondary studies
  - Collect EHR data, provide biospecimen(s) and survey, and complete a baseline exam
- Two methods of **enrollment**
  - Direct volunteers: anyone can sign up
  - Healthcare provider organizations (incl. FQHCs): diverse participants, robust EHRs, participant follow-up
- Substantial **participant engagement** in development, implementation, governance

NIH National Institute of Neurological Disorders and Stroke

Sign up for updates at: https://www.nih.gov/precisionmedicine

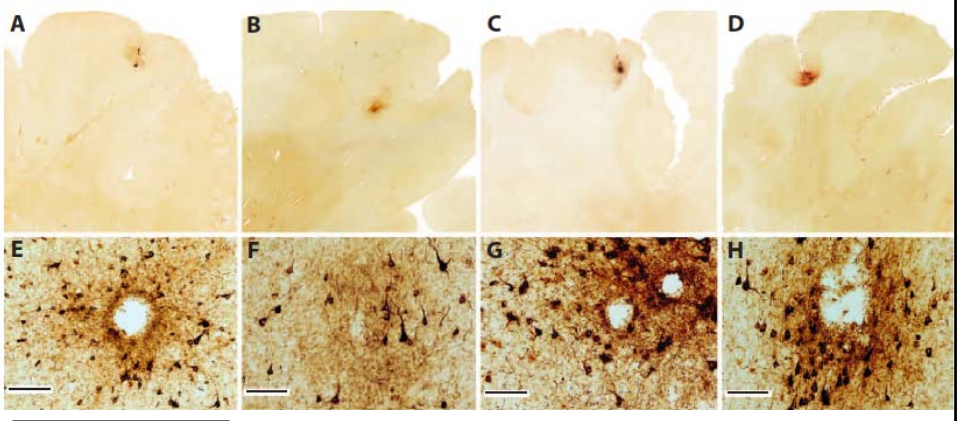
What is the NeuroBioBank?

NIMH National Institute of Mental Health

- A federated brain and tissue repository network integrated by an IT system (https://neurobiobank.nih.gov)
- Brain and tissue repositories are now being supported with contracts (NIMH, NINDS and NICHD)
- Focus on quality management, sharing, outreach

119

Punctate Cortical Regions with Phosphorylated Tau Proteins in Neurons



45 y.o.veteran with blast exposure 2 yrs ago and prior concussion

34 y.o.veteran with 2 blast exposures 6 yrs ago.

18 y.o amateur football player with multiple concussions.

21 y.o amateur football player with multiple concussions.

NIH National Institute of Neurological Disorders and Stroke

Goldstein L et. al. *Sci Transl Med* 4:134, 2012

NINDS Research Program Award (R35)

31 grants, that will be roughly $24-25M

- Program Goals
  - Provide freedom for investigators to pursue longer range, innovative, or high-risk research
  - Reduce pressure to generate results quickly to renew short-term grants
  - Allow investigators flexibility to follow up on serendipitous findings and explore new areas
  - Reduce amount of time spend writing and administering multiple grant awards
- First Round of Awards
  - Awards will be made in the coming months
  - 31 grants, ~$24-25M

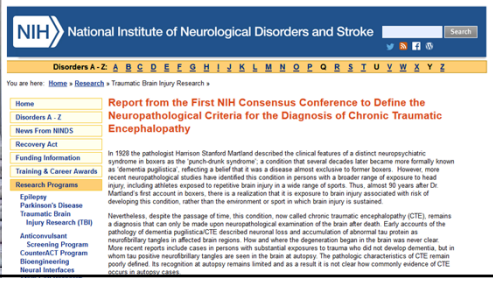
NIH National Institute of Neurological Disorders and Stroke

Criteria for Pathological Diagnosis of CTE

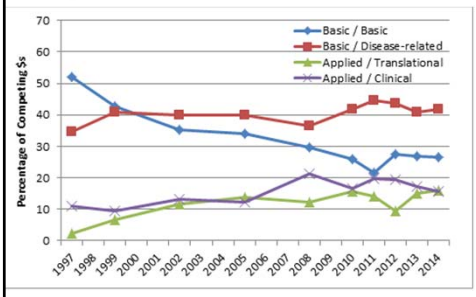
Supportive criteria for a diagnosis of CTE:
To complement the required criteria, the group also defined supportive pathological features that were frequent in CTE brains, especially in the more severely affected cases. These include:

1. Macroscopic abnormalities in the septum pellucidum (cavum, fenestration), disproportionate dilatation of the IIIrd ventricle or signs of previous brain injury;
2. Abnormal tau immunoreactive neuronal lesions affecting the neocortex predominantly in superficial layers 2 and 3 as opposed to layers 3 and 5 as in AD;
3. Abnormal tau (or silver-positive) neurofibrillary lesions in the hippocampus, especially in CA2 and CA4 regions, which differ from preferential involvement of CA1 and subiculum in AD;
4. Abnormal tau immunoreactive neuronal and astrocytic lesions in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum and substantia nigra, and
5. Tau immunoreactive in thorny astrocytes in subpial periventricular and perivascular locations.

http://www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm



NINDS Support of "Basic-Basic" Research



New NINDS Funding Announcement Aims to Spur Basic Neuroscience Research

Earlier this year, Dr. Landis and I wrote a blog post and accompanying editorial about the importanc robust portfolio of basic neuroscience research. This week, NINDS released a funding opportunity (FOA) designed as a call for applications for basic research that is not explicitly disease-related – res addresses questions involving the development, structure and/or function of the normal nervous syste

Through this FOA, we hope to underscore our commitment to investigator-initiated basic neuroscienc goal for the FOA is twofold: to stimulate more basic research applications that can be funded within o fund up to 12 additional applications each year with scores outside the pay line using a set-aside of u year for the duration of this FOA.

Reflecting the broad-based dedication to basic research across the NIH neuroscience community, NI have also committed funds and signed on to this announcement. Applications will be reviewed in the sections within the NIH Center for Scientific Review (CSR).

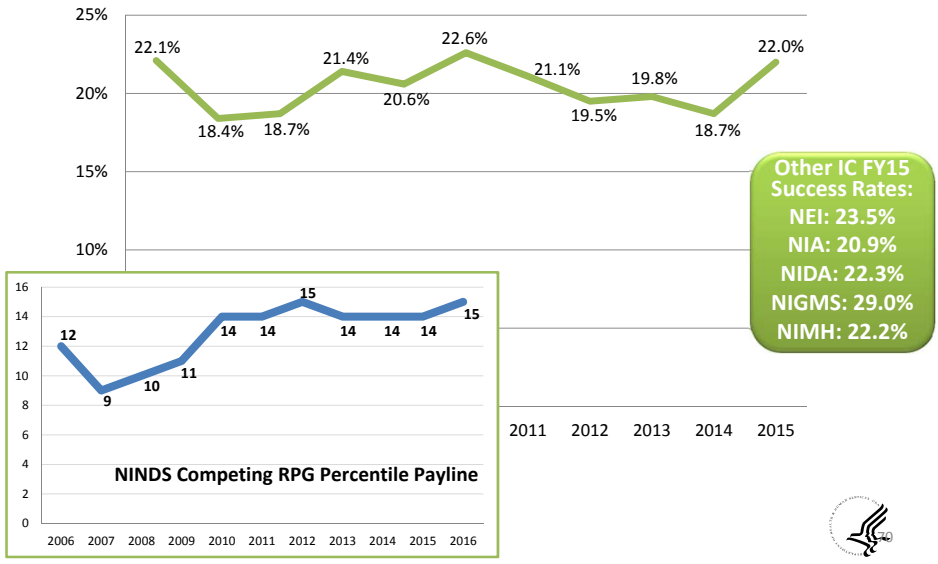
Why the new FOA?

Our initial blog post on this topic presented an analysis of NINDS funding patterns and revealed a str funding for basic research. This decline was especially pronounced for "basic/basic" research focuse

NIH National Institute of Neurological Disorders and Stroke

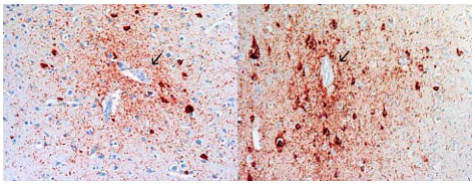
- March 2014, announced findings of research funding trend analysis
- November 2014 released funding opportunity
- PAS-15-029 Promoting Research in Basic Neuroscience (R01)
  - Goal: to stimulate increased research applications addressing fundamental questions in basic neuroscience
  - NIA, NIDA, NIMH also signed on
  - Open date: Jan. 5
- NINDS provides $5 million/year
- NINDS continues to monitor funding trends carefully

NINDS Success Rate

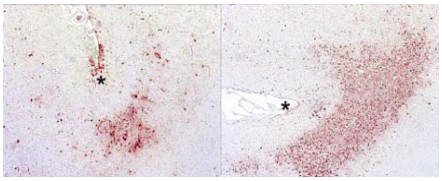


Criteria for Pathological Diagnosis of CTE

- NIH Consensus Conference (*Boston, Feb 2015*)
- In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci.



Tau antibody staining of neurons and neurites in perivascular pattern (arrow pointing to blood vessel).



Lower field photo illustrating the focal nature of the tau staining at depth of sulci (asterisk at bottom of sulcus).

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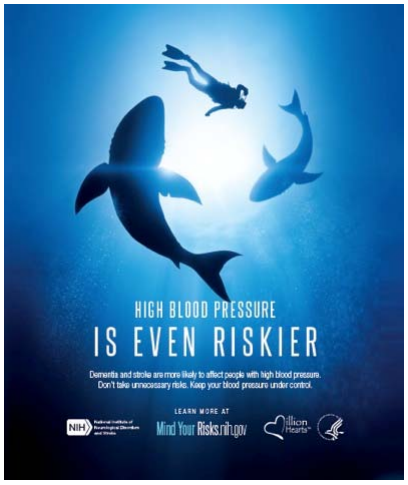
Mind Your Risks
A New NINDS Public Education Campaign



- Raise awareness among middle-aged people with hypertension that controlling blood pressure may decrease risk for dementia, as well as stroke, in later life
- Provide scientific evidence for doctors who wish to discuss this topic with their patients
- Campaign launched with PSA placement in Stroke Belt States
- NINDS-led campaign in partnership with Million Hearts®, NHLBI and NIA

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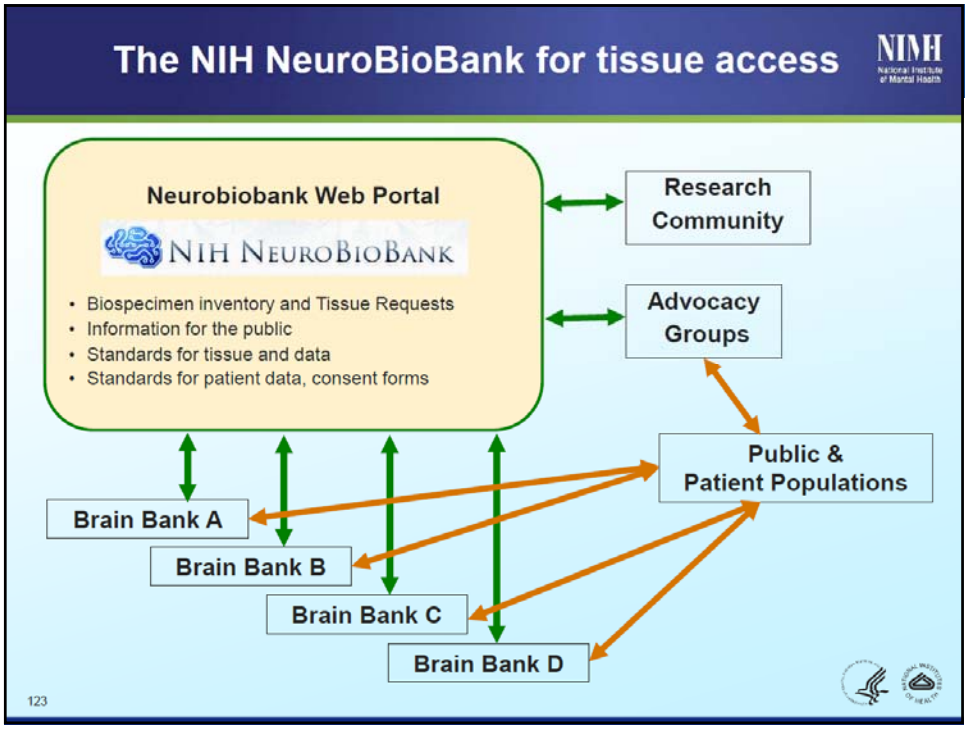
Neuroscience Training: *What's Changed?*

- Neuroscience is expanding in multiple directions
- Numbers of graduate students increased dramatically
- Time to independence increased dramatically
- Tools have become more sophisticated, and an increased degree of sophistication is needed for data analysis
- New emphasis on attracting scientists from outside biology
- New emphasis on rigor in experimental design and statistical analysis
- Funding climate became much more competitive during the 12 flat budget years and concern that associated pressures led to decline in career mentoring
- Early movement within BRAIN initiative to adapt a more "physics-like" model to engage team science to attack problems
  - Data platforms and data sharing
- Concern that attempts to increase diversity in trainees not translating as well as hoped into diversity in the academic science workforce

Increase Access to Human Tissues for Neuroscience Research

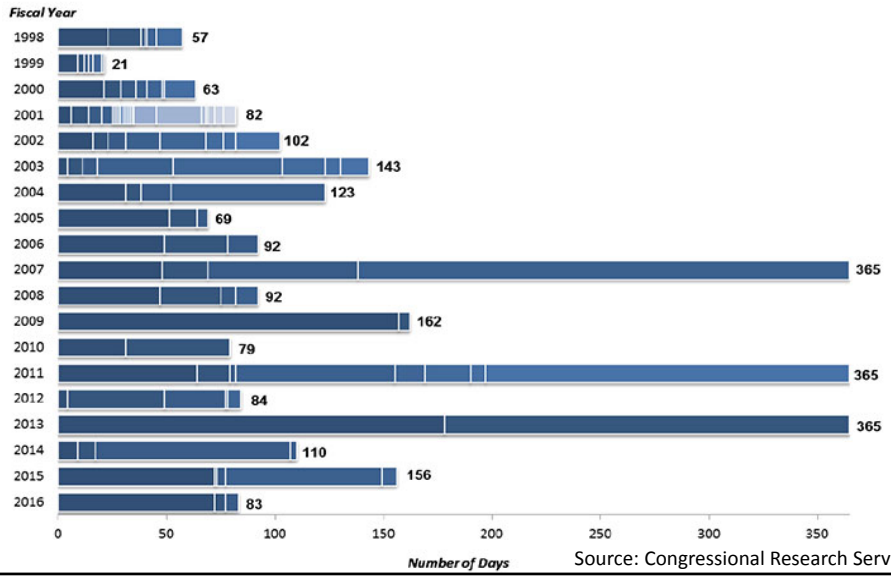
- Need ability to secure donations throughout the country via network of donors
- Increase public awareness/prospective donation
- Partner with disease advocacy communities and local medical examiners (ME) to increase donation
- Increase diversity of donor pool

NIH National Institute of Neurological Disorders and Stroke



Recent History of Continuing Resolutions

Figure 1. Duration of Continuing Resolutions (CRs): FY1998-FY2016

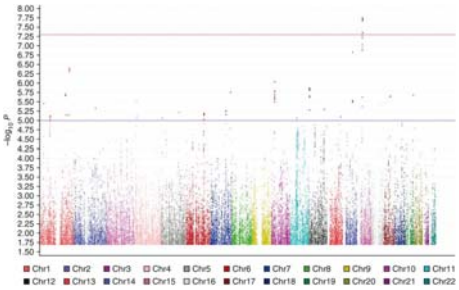


Source: Congressional Research Service

The GWAS Era

Genome-wide association studies (**GWAS**) have identified **hundreds of common DNA variants** associated with multiple **complex diseases and traits**.

>2/3 GWAS SNPs lie in noncoding regions (e.g. intergenic, introns).



Causal mechanism?
Causal gene/s?

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StrokeNet: Decreasing the Burden of Stroke

- Increase trial **efficiency**
  - Decreases time to finish studies
- **Balanced**, prioritized set of early phase 2 and phase 3 trials in prevention, treatment and recovery
- Improved research **man/woman power** in stroke research.
  - Provides stable funding for research effort, fellowship training
- Improved **data sharing**
  - Single data center with uniform governance for data access
- Stable infrastructure enables improved **team research** among different subspecialties
- Improved ability to work in public-private **partnerships** with non-profits, industry and international partners

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The Challenge

How do we translate new genomic findings into clinical targets?

Trait-associated DNA variant

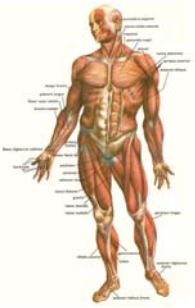
ACGG**G**CAATCA**C**GT
ACGG**G**CAATCA**C**GT
ACGG**G**CAATCA**C**GT

ACGGACAA**A**CAAGT
ACGGACAA**A**CAAGT
ACGGACAA**A**CAAGT

Open questions

Causal gene/s?
Causal mechanism?
Causal tissue/s?
Causal pathway/s?

Complex disease



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Modified from Dr. Ardlie - The Broad Institute

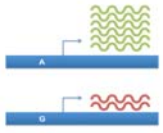
The Opportunity

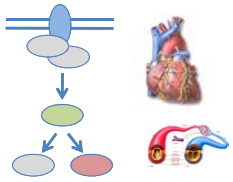
Beyond the GWAS Era

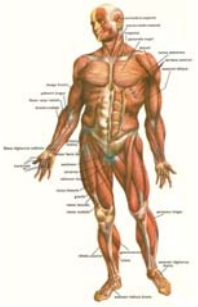
Trait-associated DNA variant → eQTL → Causal genes? Causal mechanisms? Causal tissues? Causal pathways? → Complex disease

ACGG**G**CAATCA**C**GT
ACGG**G**CAATCA**C**GT
ACGG**G**CAATCA**C**GT

ACGGACAA**A**CAAGT
ACGGACAA**A**CAAGT
ACGGACAA**A**CAAGT







Hypothesis: Disease-associated variants in noncoding regions may be affecting disease through gene regulation

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Modified from Dr. Ardlie - The Broad Institute

2015 GTEx Publications

RESEARCH | REPORTS

HUMAN GENOMICS

Effect of predicted protein-truncating genetic variants on the human transcriptome

Manuel A. Rivas, Matti Pirinen, Donald F. Conrad, Monkol Lek, Emily K. Tsang, Konrad J. Karczewski, Julian B. Maller, Kimberly R. Kukurba, David S. DeLuca, Menachem Fromer, Pedro G. Ferreira, Kevin S. Smith, Rui Zhang, Fengmei Zhao, Eric Banks, Ryan Poplin, Douglas M. Ruderfer, Shaun M. Purcell, Taru Tukiainen, Eric V. Minikel, Peter D. Stenson, David N. Cooper, Katharine H. Huang, Timothy J. Sullivan, Jared Nedzel, The GTEx Consortium, The Geuvadis Consortium, Carlos D. Bustamante, Jin Billy Li, Mark J. Daly, Roderic Guigo, Peter Donnelly, Kristin Ardlie, Michael Sammeth, Emmanouil T. Dermitzakis, Mark I. McCarthy, Stephen B. Montgomery, Tuuli Lappalainen, Daniel G. MacArthur

stability in postmortem samples. These signatures are dominated by a relatively small number of genes—which is most clearly seen in blood—though few are exclusive to a particular tissue and vary more across tissues than individuals. Genes exhibiting high interindividual expression variation include disease candidates associated with sex, ethnicity, and age. Primary transcription is the major driver of cellular specificity, with splicing playing mostly a complementary role; except for the brain, which exhibits a more divergent splicing program. Variation in splicing, despite its stochasticity, may play in contrast a comparatively greater role in defining individual phenotypes.

sequences of genetic variation, and how it affects titative traits, remains a critical challenge for sis of RNA sequencing data from 1641 samples luals, generated as part of the pilot phase of the x) project. We describe the landscape of gene thousands of tissue-specific and shared regulatory eQTL) variants, describe complex network relationship and identify signals from genome-wide association studies explained by eQTLs. These findings provide a systematic understanding of the cellular and biological consequences of human genetic variation and of the heterogeneity of such effects among a diverse set of human tissues.

National Institute of Neurological Disorders and Stroke

GTEx Completed!

Neurological Disorders: It's the brain

ALS ASSOCIATION

fyi ... for your information

Donation of Tissue for Research

Consider giving the most precious gift

VA Biorepository Brain Bank

What is the Department of Veterans Affairs (VA) Biorepository Brain Bank?

VABBB

The VA Biorepository Brain Bank (VABBB) is a human tissue bank that collects, processes, stores and gives out research specimens for future scientific studies. Presently, the VABBB is obtaining neurologic tissue specimens from Veterans who suffer from amyotrophic lateral sclerosis (ALS) or its related forms, such as primary lateral sclerosis (PLS), progressive bulbar palsy (PBP), and progressive muscular atrophy (PMA).

National Institute of Neurological Disorders and Stroke

IT TAKES BRAINS is the outreach program of the Autism BrainNet, a new network of research institutions that will collaborate on groundbreaking brain research. Brain study is the key to solving autism, and our mission is to urge families to make the heroic decision to register for brain tissue donation.

CNRM BRAIN TISSUE REPOSITORY

Center for Neuroscience and Regenerative Medicine Brain Tissue Repository

Caring for America's Veterans, So No One Stands Alone

nasr north american sudep registry

MEDICAL RESEARCH & TISSUE DONATION

The purpose of the SUDEP Registry is to collect information about people with epilepsy who have died unexpectedly, to determine if they died from SUDEP or other causes, and to collect DNA and tissue for scientific studies about the causes of SUDEP

What is Concussion?

"TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force."

SPECIAL COMMUNICATION

Position Statement: Definition of Traumatic Brain Injury

David K. Menon, MD, PhD, Karen Schwab, PhD, David W. Wright, MD, Andrew I. Maas, MD, PhD, on behalf of The Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health

NIH National Institute of Neurological Disorders and Stroke

Human Tissues and Organs Resource for Research (HTORR)

- Supported by the NIH Office of the Director through the Office of Research Infrastructure Programs
- 2013 – NDRI awarded $6,865,689 (five year award) to continue funding the recovery and distribution of human organs and tissues for medical research.
  - A core grant from the NIH Office of the Director
  - Supplemented with additional funding from:
    - National Center for Advancing Translational Sciences (NCATS)
    - National Eye Institute (NEI)
    - National Heart, Lung, and Blood Institute (NHLBI)
    - National Institute of Allergy and Infectious Diseases (NIAID)
    - National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
    - National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
    - National Institute of Mental Health (NIMH)

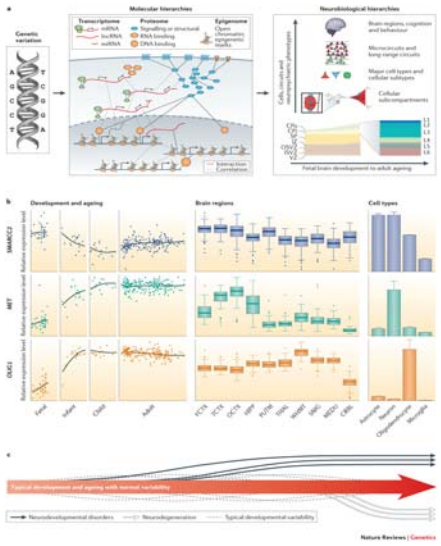
84

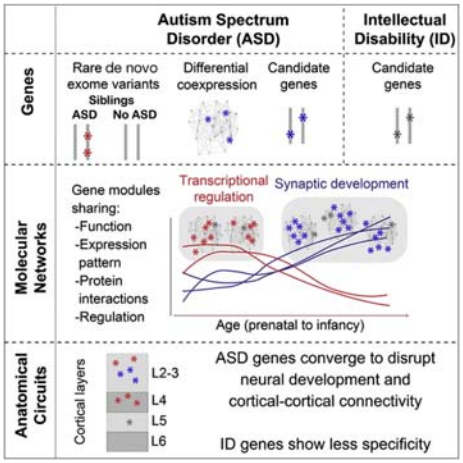
Systems biology and gene networks in neurodevelopmental and neurodegenerative disorders

Neelroop N. Parikshak[1,2], Michael J. Gandal[1,3] and Daniel H. Geschwind[1–4]

Integrative Functional Genomic Analyses Implicate Specific Molecular Pathways and Circuits in Autism

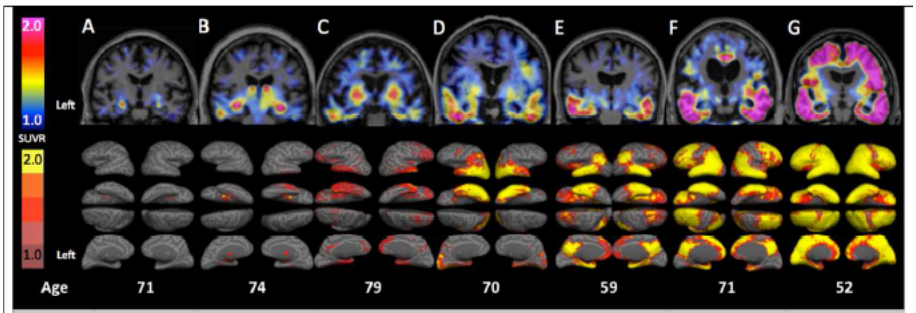
Neelroop N. Parikshak,[1,2] Rui Luo,[3,4] Alice Zhang,[2] Hyejung Won,[1] Jennifer K. Lowe,[1,4] Vijayendran Chandran,[5] Steve Horvath,[3,6] and Daniel H. Geschwind[1,2,3,4,5,*]





Molecular Brain Imaging: The future

Tau PET scanning in persons with and without Alzheimer's dementia



Age	71	74	79	70	59	71	52
MMSE	30	30	29	27	26	23	11
PiB (DVR)	Low (1.0)	High (1.2)	High (1.8)	High (1.5)	High (1.7)	High (1.5)	High (1.5)
Dx	CN	CN	CN	MCI	MCI	AD	AD

NIH National Institute of Neurological Disorders and Stroke

HTORR History

- 1987 – NDRI first awarded a grant to support Human Tissues & Organs Resource for Research (HTORR) Program
- Goal: to provide a broad range of normal and diseased human biospecimens to investigators at the NIH and other academic institutions
- 2002 – expanded to include dedicated programs to support and advance Rare Disease and HIV research
  - *National Rare Disease Biospecimen Resource (NRDBR)*
  - Contains over 2,000 tissues representing 101 rare diseases

THE NDRI RARE DISEASE RESEARCH NETWORK

tute of Disorders

What Do We Need?

- Consensus diagnosis for CTE.
- Consensus diagnosis for single TBI chronic neurodegeneration
- Promising imaging tools for detection and diagnosis of CTE and/or TBI chronic neurodegeneration
- Estimate of prevalence in selected cohorts
- Brain donor program for population based study

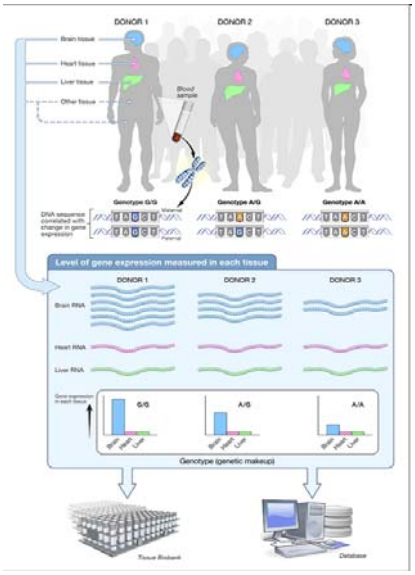
NIH National Institute of Neurological Disorders and Stroke

Chronic Pathology of Neurotrauma

- Goals:
  - Define the spectrum of chronic effects of neurotrauma and develop consensus neuropathologic criteria for chronic effects of:
    - Repetitive concussion
    - Single mild, moderate, or severe TBI
  - Search for neuroimaging correlate of chronic neuropathology after TBI by *ex vivo* imaging.
    - MRI, tau-PET
  - Better understand the prevalence of TBI-related chronic pathology in brains of persons with a variety of injury severity and exposures.
  - Exploratory studies considered high impact in peer review.

NIH National Institute of Neurological Disorders and Stroke

GTEx = Genotype-Tissue Expression



GTEx GOAL:

- to help unravel the complex interplay between genetic variation and gene expression across a wide range of non-diseased human tissues.
  - Atlas of gene expression & eQTLs
  - Biobank of tissues, DNA, RNA

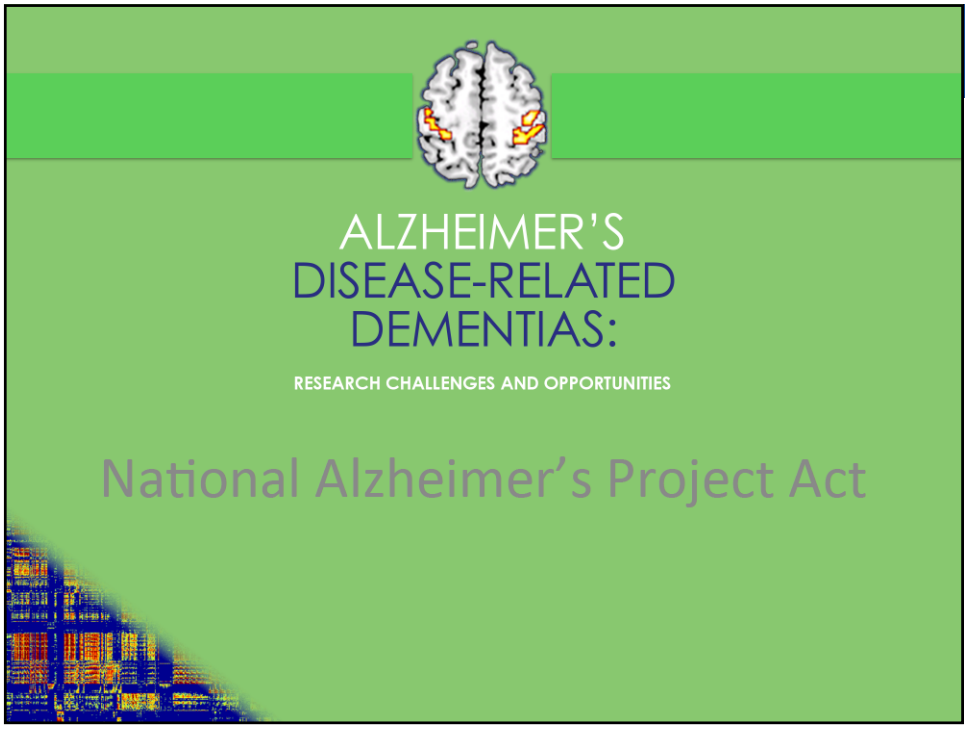
by 1/2016:

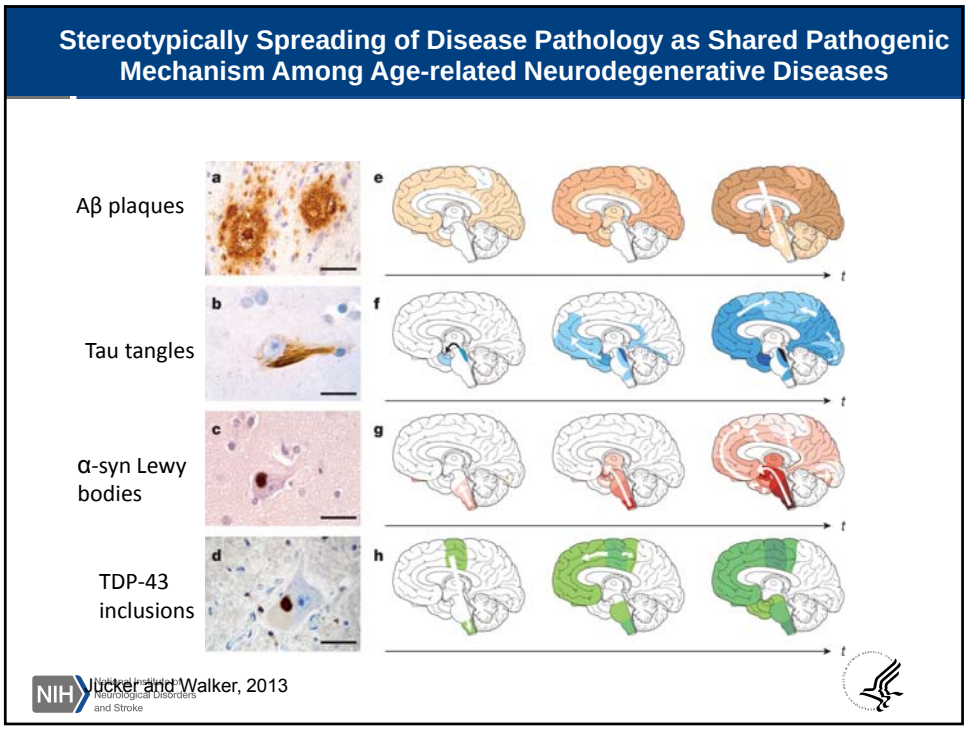
- 900 Postmortem Donors
- WES & WGS
- RNA-Seq of ~30 tissues/donor (>20,000 tissues)
- Beyond Gene Exp

NIH The Common Fund

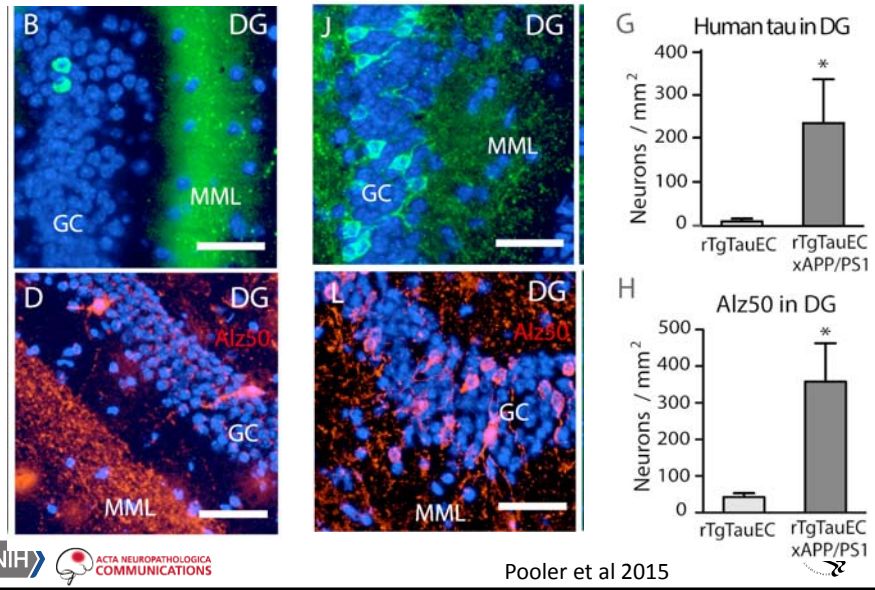
National Human Genome Research Institute

NIH National Institute of Mental Health


ALZHEIMER'S
DISEASE-RELATED
DEMENTIAS:
RESEARCH CHALLENGES AND OPPORTUNITIES
National Alzheimer's Project Act


Stereotypically Spreading of Disease Pathology as Shared Pathogenic Mechanism Among Age-related Neurodegenerative Diseases
Aβ plaques
Tau tangles
α-syn Lewy bodies
TDP-43 inclusions
a
b
c
d
e
f
g
h
t
NIH
National Institute of Neurological Disorders and Stroke
Jucker and Walker, 2013

Dramatic acceleration of tau propagation in the presence of Aβ amyloid deposits

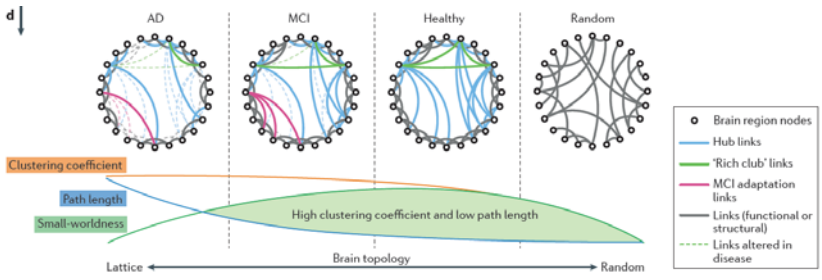


NIH ACTA NEUROPATHOLOGICA COMMUNICATIONS

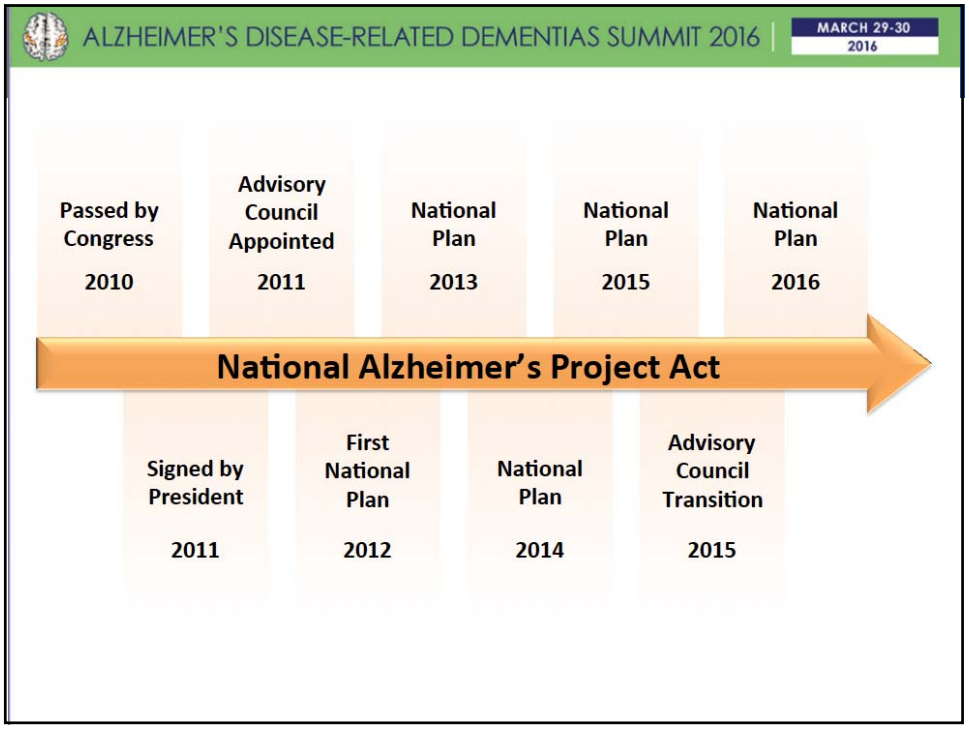
Pooler et al 2015

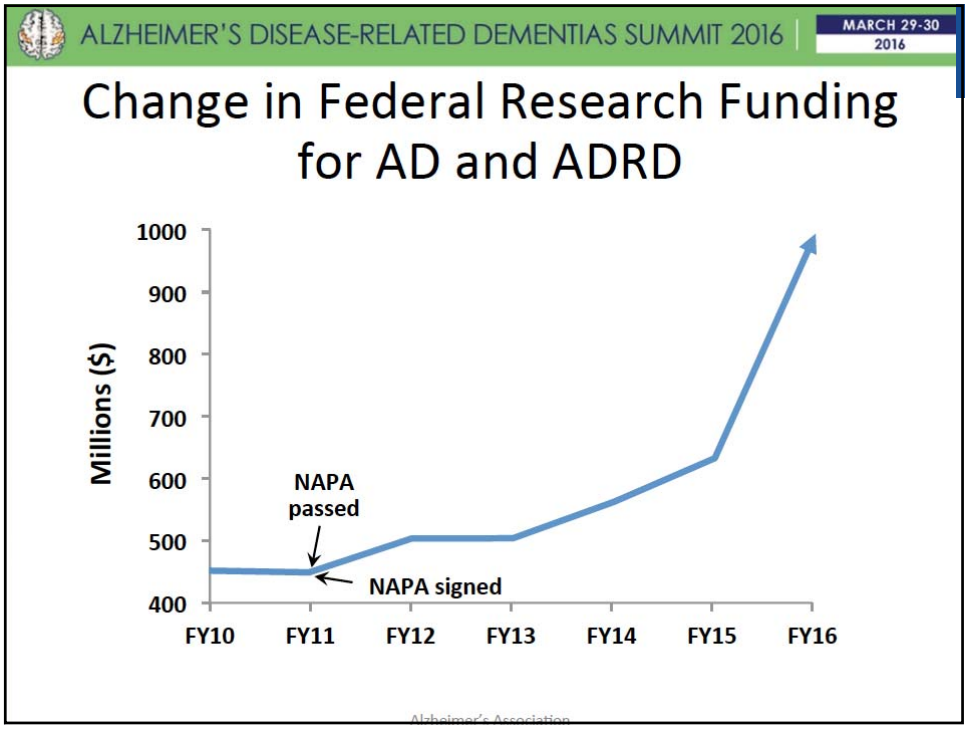
Identifying coexpression networks in tissues relevant to disease may lead to network-targeted therapies

Alzheimer's Disease Accelerated Medicine Partnership:
Mine a truly unique set of deep clinical, paraclinical, pathologic, genomic, epigenomic, and transcriptomic data assembled from frozen dorsolateral prefrontal cortex brain tissue of 1000 subjects from two cohort studies of aging and dementia.



NIH National Institute of Neurological Disorders and Stroke


ALZHEIMER'S DISEASE-RELATED DEMENTIAS SUMMIT 2016
MARCH 29-30 2016
Passed by Congress 2010
Advisory Council Appointed 2011
National Plan 2013
National Plan 2015
National Plan 2016
National Alzheimer's Project Act
Signed by President 2011
First National Plan 2012
National Plan 2014
Advisory Council Transition 2015


ALZHEIMER'S DISEASE-RELATED DEMENTIAS SUMMIT 2016
MARCH 29-30 2016
Change in Federal Research Funding for AD and ADRD
Millions ($)
1000
900
800
700
600
500
400
NAPA passed
NAPA signed
FY10
FY11
FY12
FY13
FY14
FY15
FY16
Alzheimer's Association

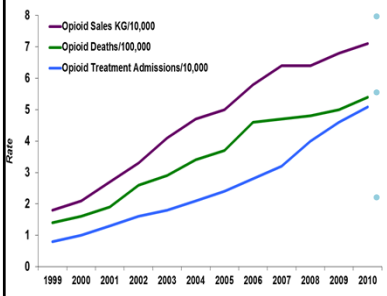
CDC Guideline for Prescribing Opioids for Chronic Pain: *Primary Care*

Clinical Questions

- Determining when to initiate or continue opioids for chronic pain
- Opioid selection, dosage, duration, follow-up, and discontinuation
- Assessing risk and addressing harms of opioid use

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

12 Recommendations



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- Non-opioid therapy is preferred for chronic pain outside of active cancer, palliative, and end-of-life care.
- When opioids are used, the lowest possible effective dosage should be prescribed to reduce risks of opioid use disorder and overdose.
- Providers should always exercise caution when prescribing opioids and monitor all patients closely.

The BRAIN Initiative®

THE BRAIN INITIATIVE®

2014 NIH BRAIN awards

- 58 awards, $46 million

2015 NIH BRAIN awards

- 67 awards, $38 million
- 130+ investigators, 8 countries outside the US

2016 NIH BRAIN awards

- Planning to make more than 100 awards, ~$150 million

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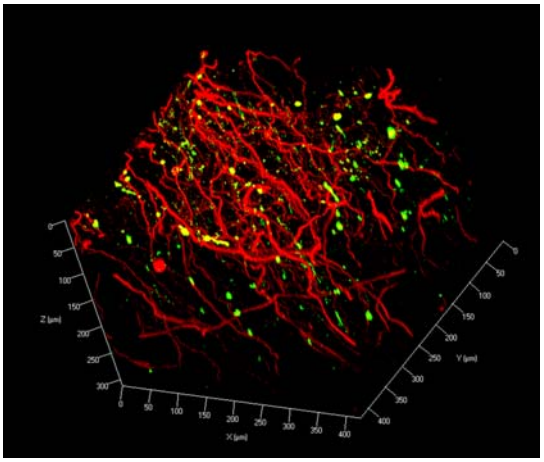
Bringing CLARITY to the human brain: visualization of Lewy pathology in three dimensions

Bringing CLARITY to the human brain: visualization of Lewy pathology in three dimensions

Z-stack image of double immunofluorescence with anti-αSN (green) and anti-TH (red) antibodies on human midbrain block (z-stack step size 1.5 μm).



Neuropathology and Applied Neurobiology
7 DEC 2015 DOI: 10.1111/nan.12293
http://onlinelibrary.wiley.com/doi/10.1111/nan.12293/full#nan12293-fig-0006

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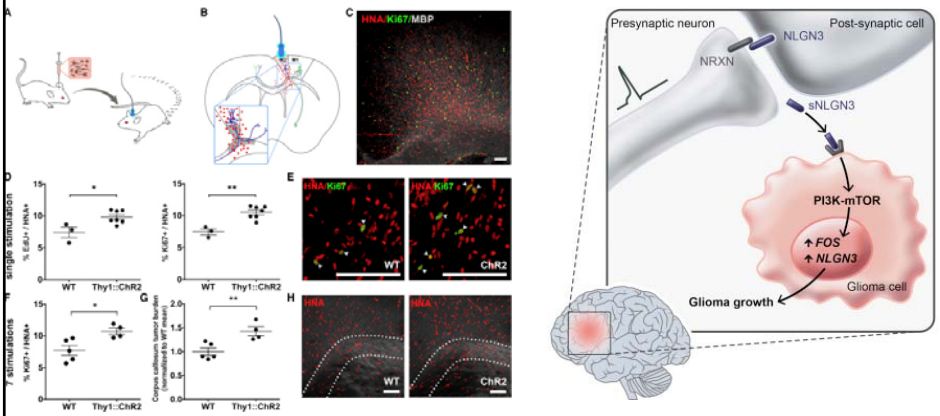
Neuronal Activity Promotes Glioma Growth through Neuroligin-3 Secretion

Humsa S. Venkatesh, Tessa B. Johung, Viola Caretti, Alyssa Noll, Yujie Tang, Surya Nagaraja, Erin M. Gibson, Christopher W. Mount, Jai Polepalli, Siddhartha S. Mitra, Pamelyn J. Woo, Robert C. Malenka, Hannes Vogel, Markus Bredel, Parag Mallick, Michelle Monje

Cell Volume 161, Issue 4, 2015, 803–816



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BRAIN Initiative: *Exciting Advances Continuing to Emerge*

frontiers in Molecular Neuroscience

LETTER

nature International weekly journal of science

Bidirectional electromagnetic control of the hypothalamus regulates feeding and metabolism

Sarah A. Stanley[1], Leah Kelly[1], Kaamashri N. Latcha[1], Sarah F. Schmidt[1], Xiaofei Yu[1], Alexander R. Nectow[1], Jeremy Sauer[2], Jonathan P. Dyke[3], Jonathan S. Dordick[2] & Jeffrey M. Friedman[1,4]

A Toolkit for Orthogonal and *in vivo* Optical Manipulation of Ionotropic Glutamate Receptors

Joshua Levitz, Andrei T. Popescu, [...], and Ehud Y. Isacoff

LETTERS

nature biotechnology

Cre-dependent selection yields AAV variants for widespread gene transfer to the adult brain

Benjamin E Deverman[1], Piers L Pravdo[1], Bryan P Simpson[1], Sripriya Ravindra Kumar[1], Ken Y Chan[1], Abhik Banerjee[1], Wei-Li Wu[1], Bin Yang[1], Nina Huber[2], Sergiu P Pasca[2] & Viviana Gradinaru[1]

Neuron

Cell

Mapping Sub-Second Structure in Mouse Behavior

Cell Stem Cell

Available online 30 March 2016

In Press, Corrected Proof — Note to users

Brief Report

Expression Analysis Highlights AXL

Entry Receptor in Neural Stem Cel

Tomasz J. Nowakowski[1, 2, 3], Alex A. Pollen[1, 2, 3], Elizabeth Di Lullo[1, 2], Carmen Sandoval-Espinosa[1, 2], Marina Bershteyn[1, 2], Arnold R. Kriegstein[1, 2]

Neuron

Inhibition, Not Excitation, Drives Rhythmic Whisking

Deschênes, Jun Takatoh,

asia Kurnikova, ...,

iro Furuta, Fan Wang,

Kleinfeld

Over 130 publications emerged from NIH BRAIN to date

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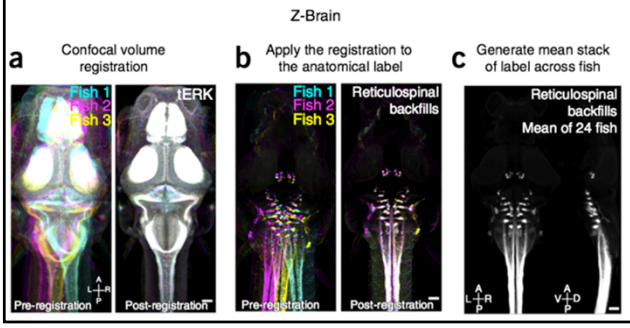
Exciting New Discoveries

Drs. Florian Engert and Alexander Schier map whole brain neural activity on the anatomical map of the zebrafish brain – "Z Brain"

- Create expandable, open-sourced atlas includes whole-brain activity patterns resulting from calcium influx associated with neuronal firing, paired with behaviors
- BRAIN award to identify form, function, and plasticity of circuits in zebrafish brain
  - Generate quantitative model of neural circuits across brain that explains dynamic processing of information and generation of motor output



Advance:

- Whole-brain activity assessed via pERK expression following behavior
- High-throughput confocal imaging to create 3D brain maps from ~900 zebrafish
- Labeling to identify 294 distinct brain regions

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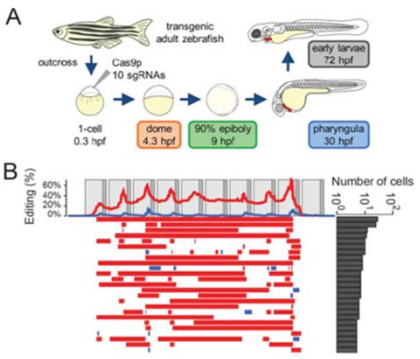
Exciting New Discoveries

Drs. Jay Shendure and Alexander Schier develop novel tool for studying cell lineages in whole organisms

Genome editing of synthetic target arrays for lineage tracing (GESTALT) tracks cell fate in complex, multicellular organisms (*Science*)

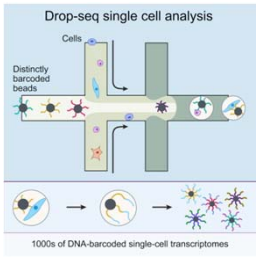
- Method uses CRISPR/Cas9 to edit a unique set of genes, called a "barcode," to mark individual cells
  - Zebrafish embryos are injected with different barcodes, and cell expression is examined at multiple developmental time points
  - Mutation patterns are used to determine lineage relationships and cell fate
- Improves ability to create a census of cell types in complex organisms
- Powerful new tool in developmental biology to study normal and abnormal development

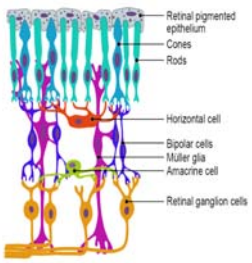


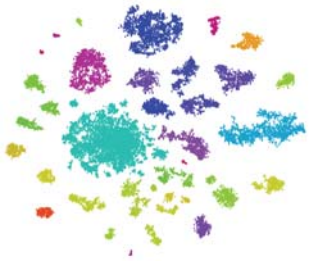
BRAIN: *Exciting New Tools*

Drop-Seq single cell analysis

- Steve McCarroll, Joshua Sanes, and colleagues, *Cell*
- Rapid, inexpensive method for classifying cells based on gene expression profiles
- Completes genome-wide gene expression in thousands of individual cells in a single experiment
- 44,808 retinal cells from mice sorted into 39 distinct populations
- This technology brings us closer to having a complete parts list for the brain







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BRAIN Initiative Alliance

NIH NSF FDA IARPA

Mission Statement: *The aim of the BRAIN Initiative Alliance is to coordinate and facilitate communications from its members related to the BRAIN Initiative.*

Short Term Focus: Launched website that serves as a single point of communication for all BRAIN Initiative-related announcements of funding opportunities and accomplishments

HHMI HOWARD HUGHES MEDICAL INSTITUTE

THE KAVLI FOUNDATION

SIMONS FOUNDATION

ALLEN INSTITUTE for BRAIN SCIENCE *Fueling Discovery*

THE BRAIN INITIATIVE®

BRAIN: *Where Are We?*

President Announces BRAIN Initiative *April 2013*

1st meeting of the BRAIN MCWG *August 2014*

1st BRAIN PI meeting *November 2014*

Neuroethics Workgroup Established *August 2015*

2nd BRAIN PI meeting *December 2015*

3rd BRAIN PI meeting *December 2016*

***BRAIN 2025* Report released** *June 2014*

1st round of NIH BRAIN awards *September 2014*

1st BRAIN Initiative Alliance discussion *July 2015*

BRAIN INITIATIVE ALLIANCE

2nd round of NIH BRAIN awards *September 2015*

Third round of BRAIN awards *October 2016*

NIH National Institutes of Health *Turning Discovery Into Health*

THE BRAIN INITIATIVE®

SFN Satellite Event

Title: BRAIN Initiative "TAD Talks:" Technology Accelerating Discovery

When: 6:30pm-8:30pm (Pacific), November 14, 2016

Sponsor: The BRAIN Initiative Alliance

NIH National Institutes of Health
Turning Discovery Into Health

107

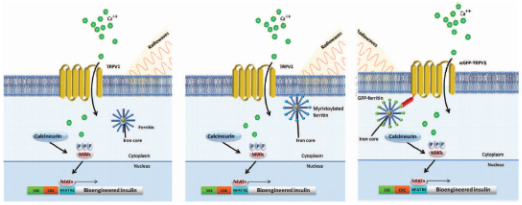
Questions?

Walter J. Koroshetz, M.D.
Director
National Institute of Neurological Disorders and Stroke
Email: koroshetzw@ninds.nih.gov
Website: http://www.ninds.nih.gov/

Follow me @NINDSdirector

108

Cell and Circuit Manipulation



Remote regulation of TRPV1 channels

Stanley, Mt. Sinai

Remote regulation by radiofrequency waves of ferritin conjugated TRPV1 channels. Stanley, Mt. Sinai

SAFETY VALIDATION OF REPEATED BLOOD–BRAIN BARRIER DISRUPTION USING FOCUSED ULTRASOUND

THIELE KOBUS,*† NATALIA VYKHODTSEVA,* MAGDALINI PILATOU,* YONGZHI ZHANG,* and NATHAN MCDANNOLD*

*Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; and †Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

(*Received* 23 *July* 2015; *revised* 29 *September* 2015; *in final form* 14 *October* 2015)

NIH National Institute of Neurological Disorders and Stroke

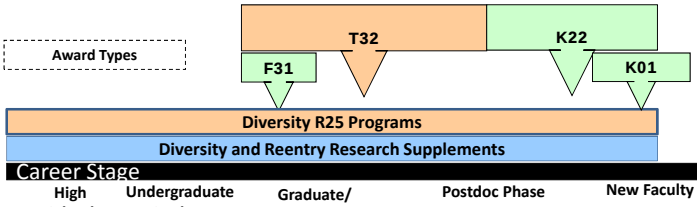
BRAIN Funding in FY2017: *New Concepts*

Brain Cell Types	Tools for Circuit Diagrams	Tech. to Monitor Neural Activity	Precise Inter-ventional Tools	Theory and Data Analysis Tools	Advance Human Neuroscience	Integrate Approaches

Funding Opportunity Concepts for FY17 Include:

- Comprehensive & Specialized Cell Phenotyping Centers (+ Phase2)
- Selected Cell Phenotyping Projects for Human/Non-human Primate Cell Classification (U01)
- BRAIN Data Centers for Cell Phenotyping, Integrated approaches, and Human recording (U24)
- Development of Next-Generation Human Brain Imaging Tools and Technologies: + Phase II (U01), and Human Recording Consortia with data hubs.
- BRAIN Initiative Fellows Training Grant (F32)
- Research Career Enhancement Award (K18)
- Targeted Integrated Approaches Research Projects Phase 2 (U01)
- Exploratory Targeted Integrated Approaches Research Projects (U01)

NINDS Diversity Scientific Training and Career Opportunities



Diversity F31 – Predoctoral

Diversity NINDS K22 – Postdoc to Faculty Transition Award

Diversity NINDS K01 –New Tenure Track Faculty

T32 – Institutional Research Training Grant recruitment and retention plans to enhance diversity

NIH Summer R25 - High School and Undergraduate Students

NIH Blueprint ENDURE R25 – pairs diverse undergraduates with neuroscience focused T32 programs

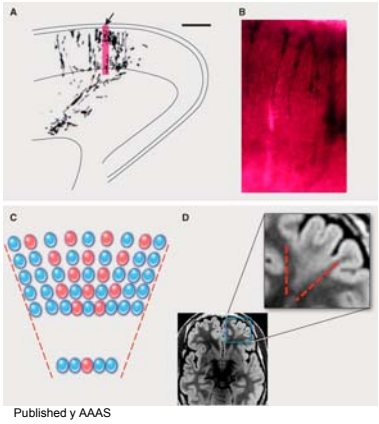
NINDS Neuroscience Development for Advancing the Careers of a Diverse Research Workforce R25- Supports educational programs designed to attract, train, and further the career of diverse graduate, postdoc and junior faculty

Research Supplements to Promote Diversity in Health-Related Research :
under-represented racial and ethnic backgrounds
individuals from disadvantage socioeconomic backgrounds
people with disabilities
people reentering research

NIH Neurological Disorders and Stroke

Somatic Mutation in BRAIN; Chris Walsh Boston Children's Hospital

Focal cortical dysplasia: a clonal-appearing brain lesion suspected to be caused by somatic mutation in a progenitor cell..



Published y AAAS

Annapurna Poduri et al. Science 2013;341:1237758

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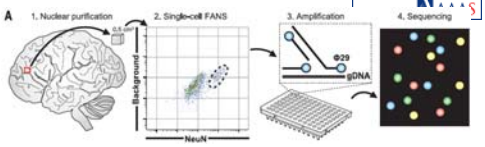
Somatic mutation in single human neurons tracks developmental and transcriptional history

Science



- Somatic single nucleotide variants are found commonly in brain.
- SNVs are most common in coding exons
- Strand bias suggests that SNVs occur in transcriptionally active genes.
- SNVs correlate with epigenetic markers of transcription
- Suggests that transcriptional-related damage to DNA occurs "use it and loose it "

Degenerative change — Chronic Traumatic Encephalopathy (CTE)

- Progressive degenerative disease
- Dementia pugilistica "punch-drunk syndrome"
- Post-mortem diagnosis
  - Nerve cell loss
  - Accumulation of tau protein/neurofibrillary tangles
- Repetitive brain injury raises the risk

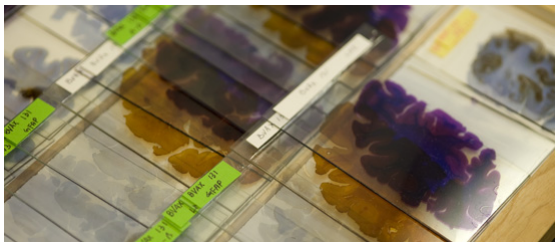


Image: http://www.bumc.bu.edu/supportingbusm/research/brain/cte/

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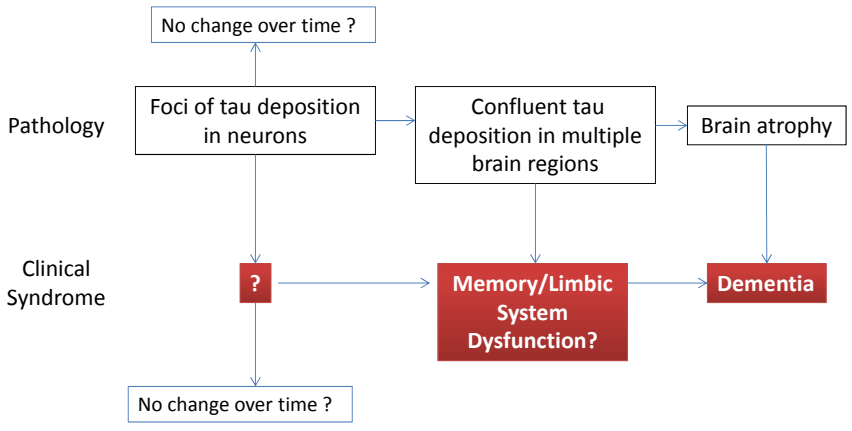
Degenerative change — Chronic Traumatic Encephalopathy (CTE)



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BIG Questions Remain

1. What are the underlying **mechanisms** of post-concussive syndrome?
2. What are the underlying mechanisms of increased **vulnerability** to prolonged post concussive syndrome with repeated concussion?
3. What **dose** of TBI *(e.g., number, intensity, temporal pattern, regional factors)* is associated with foci of tau deposits?
4. How does tau deposition **evolve** to affect widespread brain regions. *(e.g., spread vs. different regional rates of neurodegenration)*?
5. Given similar exposures, how can we **predict** an individual's risk for CTE? *(e.g., genetics, environmental influences, lifestyle, etc.)*

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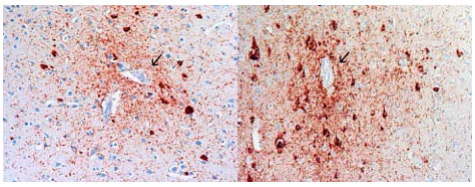
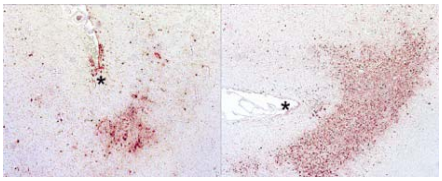
Criteria for Pathological Diagnosis of CTE

- NIH Consensus Conference (*Boston, Feb 2015*)
- In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci.



Tau antibody staining of neurons and neurites in perivascular pattern (arrow pointing to blood vessel).



Lower field photo illustrating the focal nature of the tau staining at depth of sulci (asterisk at bottom of sulcus).

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