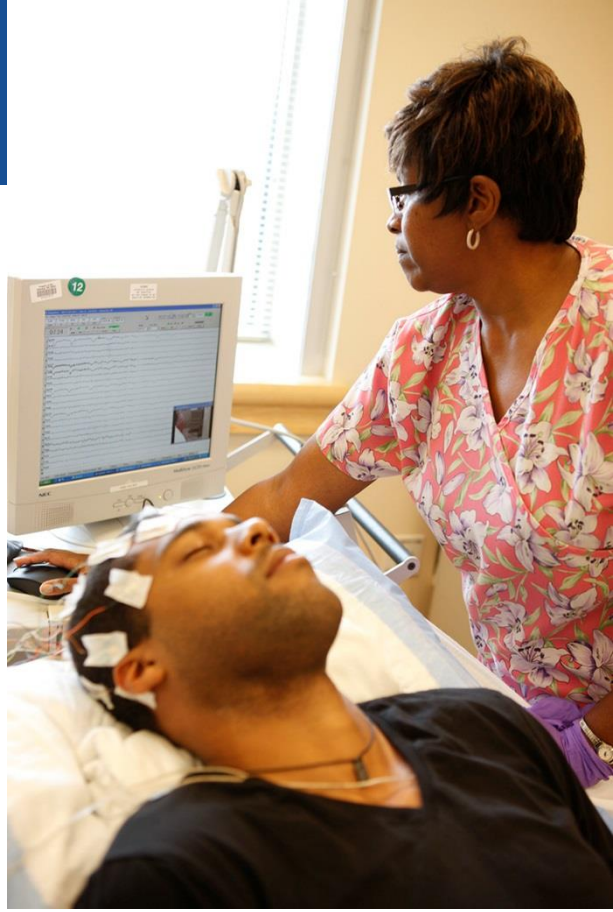
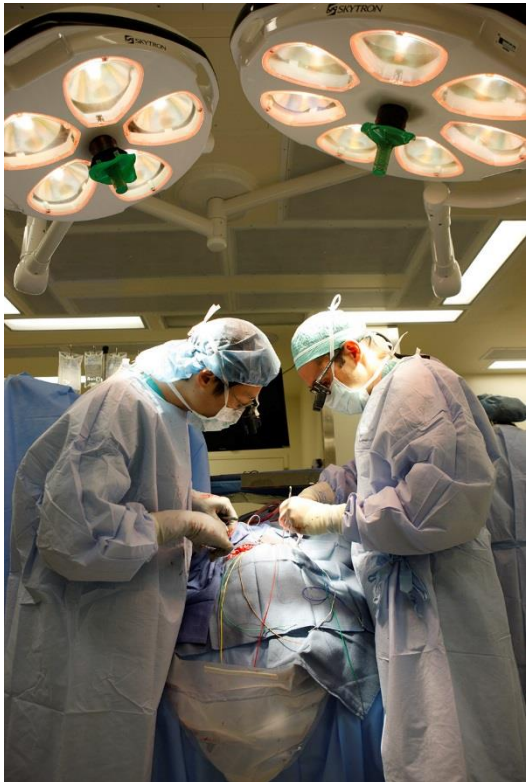
National Institute of Neurological Disorders and Stroke

Interagency Collaborative to Accelerate Research on Epilepsy (ICARE)

April 26, 2019

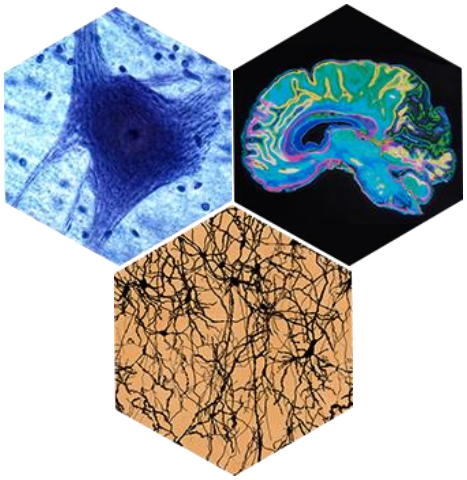
Walter J. Koroshetz, M.D.
Director, National Institute of Neurological Disorders and Stroke, NIH





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 in basic, translational and clinical research
- Identify gaps in research and public health needs
- Train a talented and diverse research workforce
- Support development of tools and resources to enable discoveries
- Communicate and collaborate with all stakeholders, including the public
- Evaluate and continuously improve all NINDS programs

Appropriation History

(Dollars in Thousands)

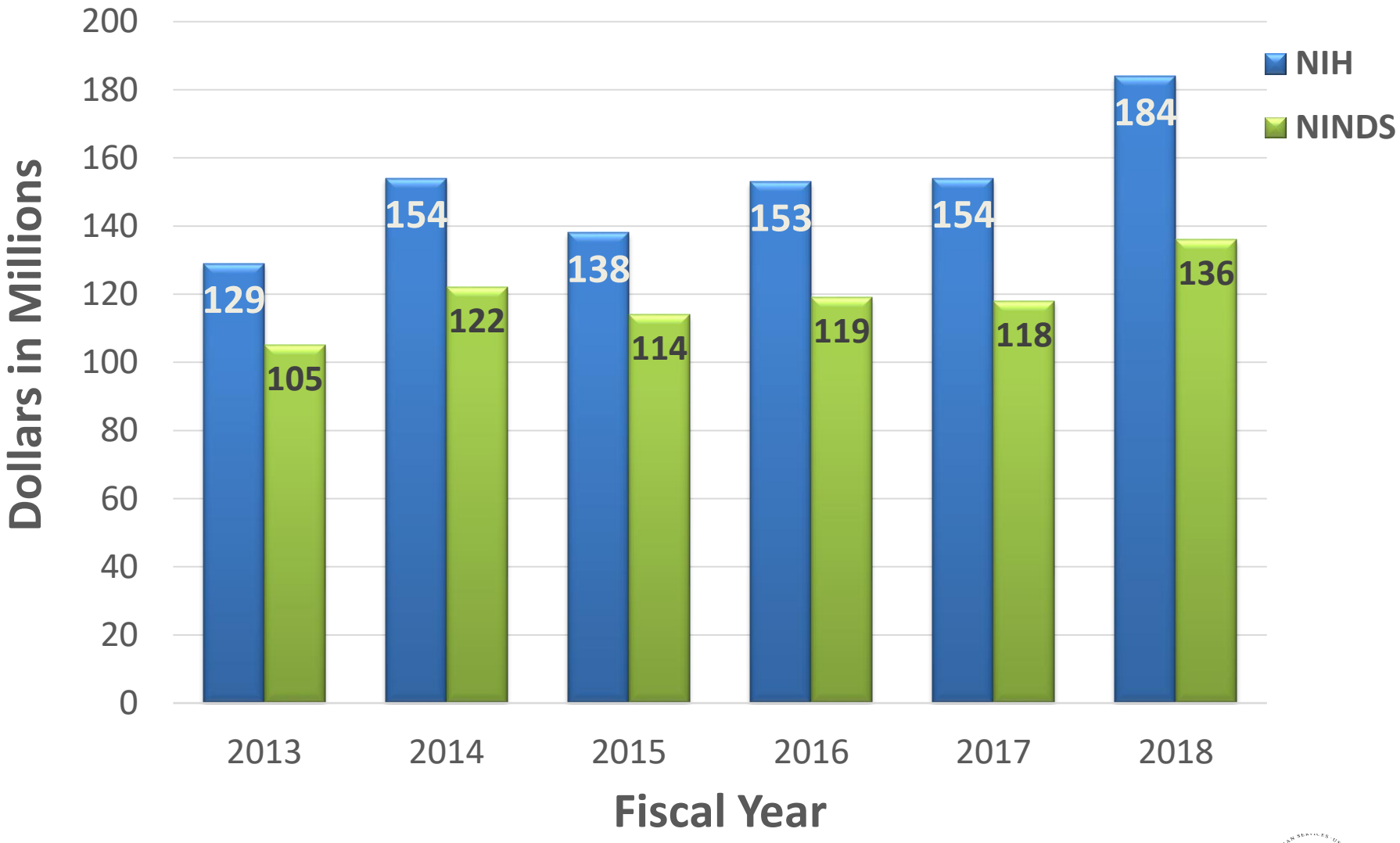
	FY 2013	FY2014	FY 2015	FY 2016	FY 2017	FY 2018	FY 2018 with Opioid and Cures	FY 2019 Appropriation	FY 2019 with Opioid and Cures
NINDS	$1,533,795	1,588,904	1,604,607	1,692,833	1,778,688	1,888,130	2,188,149	1,966,913*	2,274,413
NINDS % Change	-5.6%	3.6%	1.0%	5.5%	5.4%	6.15%	23%	4.17%	3.9%
NIH	$29,151,462	30,150,853	30,311,349	32,345,549	34,161,349	36,228,080	37,224,080	38,023,000**	39,234,000
NIH % Change	-5.5%	3.4%	0.5%	6.7%	5.6%	6%	8.9%	4.9%	5.4%

- NIH FY 2019 Appropriation with Opioid and Cures is a $2 billion increase over FY 2018's level.
- In FY 2019, NINDS received $250m for Pain Research in part of the HEAL Initiative and $57.5m in CURES Act fund for the BRAIN Initiative.
- In FY 2018, NINDS co-managed approximately $100 million of the AD/ADRD monies that NIA received. In FY 2019, NINDS expects to co-manage more than $140m of the AD/ADRD monies under an MOU with NIA.

* The **FY 2019 Appropriation** column does not include the monies that NINDS received for the HEAL Initiative ($250m) and CURES Act ($57.5m).

** The **FY 2019 Appropriation** column does not include the monies that NIH received for the HEAL Initiative ($500m) and CURES Act ($711m).

NIH and NINDS Funding for Epilepsy Research



https://report.nih.gov/categorical_spending.aspx

NINDS Contributions: Brain stimulation therapies for epilepsy

NINDS Contributions to Approved Therapies

https://www.ninds.nih.gov/About-NINDS/Impact/NINDS-Contributions-Approved-Therapies/Brain-stimulation-therapies-epilepsy

Development Timeline

NIH Support

1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015

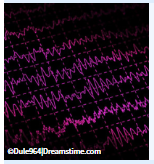
1954 During recordings of brain activity in people with epilepsy undergoing surgery, Wilder Penfield and Herbert Jasper observe that seizure-like activity could be halted with brief counter stimulation[1].

Low frequency stimulation in the anterior nucleus of the thalamus (ANT) is reported to synchronize brain activity, while high frequency stimulation had the opposite effect[9].

1967-1972 Surgical lesions of the ANT decreased the occu of seizures in a small clinical study and in an a epilepsy[10,11].

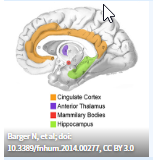
Studies initially suggest electrical stimulation in the cerebellum may reduce seizures, but carefully controlled trials by NINDS intramural investigators and others show no clear benefit[4,5,6,7,8].

1980-1987 Small, unblinded studies show chronic ANT s seizure control in people with medically refra While promising, these early studies used ext were inconvenient to patients.



The first systems emerge for automated seizure detection based on EEG recordings of brain activity.[30]

1983-1999 Brief bursts of stimulation are shown to termi seizure-like activity in people with epilepsy a when delivered soon after onset[25,26,27,28].

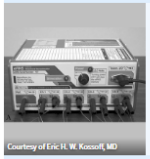


Studies to understand seizure mechanisms place the ANT within a brain circuit involved in the spread of initially localized seizures[12,13].

1991 Academic and industry investigators develop n detection algorithms that will be adapted for u responsive stimulation devices[31,32,33,34].

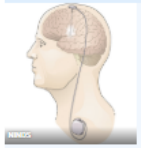
High frequency stimulation in the ANT is shown to protect against generalized seizures in an animal model.[14]

1997 The FDA approves two new implantable neurostimulation devices: Medtronic's deep brain stimulation (DBS) system as a treatment for tremor and Cyberonics' vagal nerve stimulator for medically refractory epilepsy[18,19].



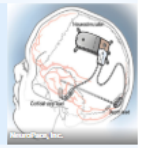
Initial tests of responsive stimulation for safety and feasibility used prototypes with external neurostimulators in people undergoing evaluation for epilepsy surgery[35,36,37].

2002-2004 Pilot studies report improved seizure control with chronic bilateral ANT stimulation using Medtronic's implantable deep brain stimulation (DBS) system[20,21].



2010-2015 The SANTE (Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy) trial and a seven-year follow up period show lasting reductions in seizure frequency in those who were treated and meaningful improvements in quality of life[22,23].

2011 The pivotal clinical trial of the NeuroPace responsive neurostimulation system (RNS®) shows that seizure frequency decreased in individuals receiving stimulation[39].



2013 The NeuroPace RNS® receives approval from the FDA for use in adults with medically refractory focal epilepsy.[40]

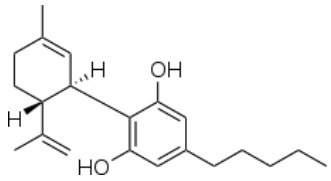
2018 Medtronic's DBS System for Epilepsy receives approval from the FDA for use in adults with medically refractory focal epilepsy[24].

National Institute of Neurological Disorders and Stroke

FDA Approvals in Epilepsy

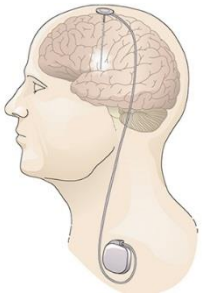
FDA Approves Cannabidiol (CBD) for Dravet Syndrome and Lennox Gastaut

- Approved by FDA as Epidiolex® (GW Pharmaceuticals) in June 2018

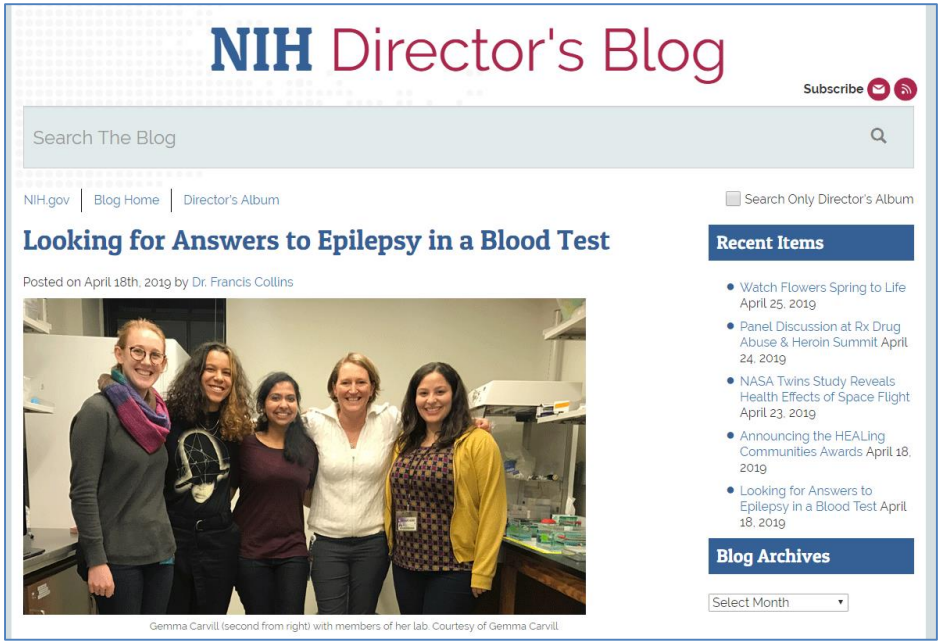


FDA Approves Deep Brain Stimulation (DBS) for Epilepsy

- DBS Therapy by Medtronic was approved for epilepsy in May 2018



2018 NIH New Innovator Award: Blood Tests for Epilepsy



NIH Director's Blog

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Looking for Answers to Epilepsy in a Blood Test

Posted on April 18th, 2019 by Dr. Francis Collins

Gemma Carvill (second from right) with members of her lab. Courtesy of Gemma Carvill.

Recent Items

- Watch Flowers Spring to Life April 25, 2019
- Panel Discussion at Rx Drug Abuse & Heroin Summit April 24, 2019
- NASA Twins Study Reveals Health Effects of Space Flight April 23, 2019
- Announcing the HEALing Communities Awards April 18, 2019
- Looking for Answers to Epilepsy in a Blood Test April 18, 2019

Blog Archives

Select Month

1DP2NS111506-01

JOURNAL OF NEUROGENETICS
2018, VOL. 32, NO. 4, 295–312
https://doi.org/10.1080/01677063.2018.1513509

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Check for updates

Unravelling the genetic architecture of autosomal recessive epilepsy in the genomic era

Jeffrey D. Calhoun and Gemma L. Carvill

Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Cell-free DNA Sequencing Approaches To Define The Genetic Etiology of Unexplained Epilepsy

Gemma Carvill at Northwestern University

National Institute of Neurological Disorders and Stroke

Recent NINDS-supported Advances in Epilepsy Research

JNeurosci
THE JOURNAL OF NEUROSCIENCE

TrkB-Shc signaling protects against hippocampal injury following status epilepticus

Huang et al., J Neuro. (2019)
PI: McNamara
R01 NS 056217

SCIENTIFIC REPORTS

Basu et al, Sci Rep, 2019
PI: Roopra
R21 NS095187

Histone deacetylase inhibitors restore normal hippocampal synaptic plasticity and seizure threshold in a mouse model of Tuberous Sclerosis Complex

Trina Basu[1,2], Kenneth J. O'Riordan[5], Barry A. Schoenike[1], Nadia N. Khan[1,3], Eli P. Wallace[1,4], Genesis Rodriguez[1], Rama K. Maganti[5] & Avtar Roopra[1,2,3]

ARTICLE

Cognitive phenotypes in temporal lobe epilepsy are associated with distinct patterns of white matter network abnormalities

Anny Reyes, MS, Erik Kaestner, PhD, Naeim Bahrami, PhD, Akshara Balachandra, BS, Manu Hegde, MD, PhD, Brianna M. Paul, PhD, Bruce Hermann, PhD, and Carrie R. McDonald, PhD

Correspondence
Dr. McDonald
camcdonald@ucsd.edu

Neurology® 2019;92:e1957-e1968. doi:10.1212/WNL.0000000000007370

Reyes et al, Neurol, 2019
PI: McDonald
R01 NS065838

Epilepsy Centers Without Walls (CWOW) for Collaborative Research in the Epilepsies

epi4K
GENE DISCOVERY IN EPILEPSY

Collaborative has examined genetic data from 4,000 individuals in order to understand the genes underlying epilepsy

CSR
THE CENTER FOR SUDEP RESEARCH

Brings together extensive expertise to understand Sudden Unexplained Death in Epilepsy

EpiBioS4Rx

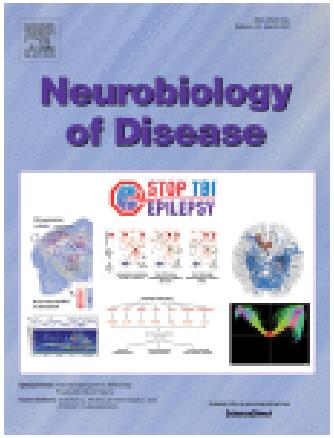
Studies of animals and patients with traumatic brain injury (TBI) leading to post-traumatic epilepsy (PTE) in order to develop future clinical trials of epilepsy prevention therapies

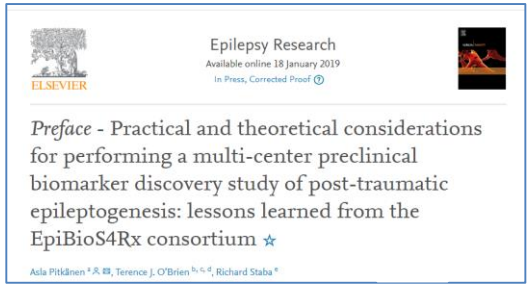
New center!– CWOW on **Functional Evaluation of Human Genetic Variants**

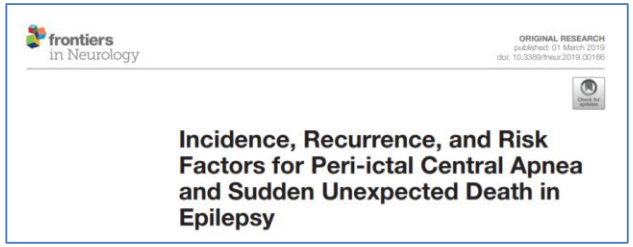
- **Dr. Alfred George at Northwestern** will direct the new Channelopathy-Associated Epilepsy Research Center
- **$12 million, 5-year project** aims to improve the accuracy of genetic diagnosis of epilepsy, and to determine the optimal drug therapy for specific mutations

CWOW FOA will be re-issued in FY 2019 to support one more center on epilepsy functional genomics

Recent Publications from the CWOWs







EpiBioS4Rx investigators

- Issue of *Neurobiology of Disease* focused on posttraumatic epilepsy following traumatic brain injury
  - Edited by Solomon L. Moshé, Jerome Engel Jr, Aristea S. Galanopoulou, Volume 123, pp 1-144 (March 2019)
- Virtual issue of *Epilepsy Research* with interim analysis of the success of procedural harmonization
  - Pitkanen, O'Brien, and Staba, *Epilepsy Research*, 2019

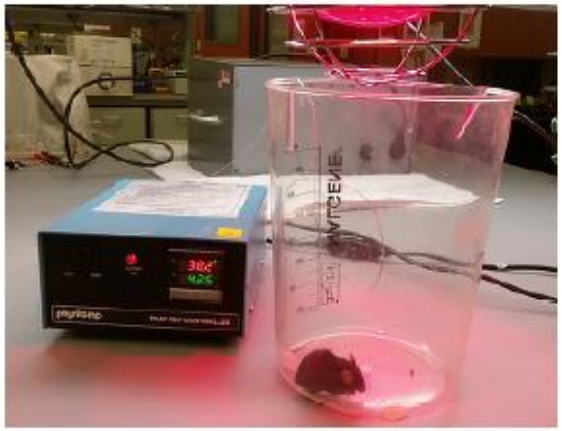
Center for SUDEP Research

- Ictal Central Apnea (ICA) incidence is almost twice the incidence of Peri-ictal central apnea (PCCA) and is only seen in focal epilepsies
  - *Vilella et al, Front. Neurol, 2019*

NINDS Epilepsy Therapy Screening Program (ETSP) Update

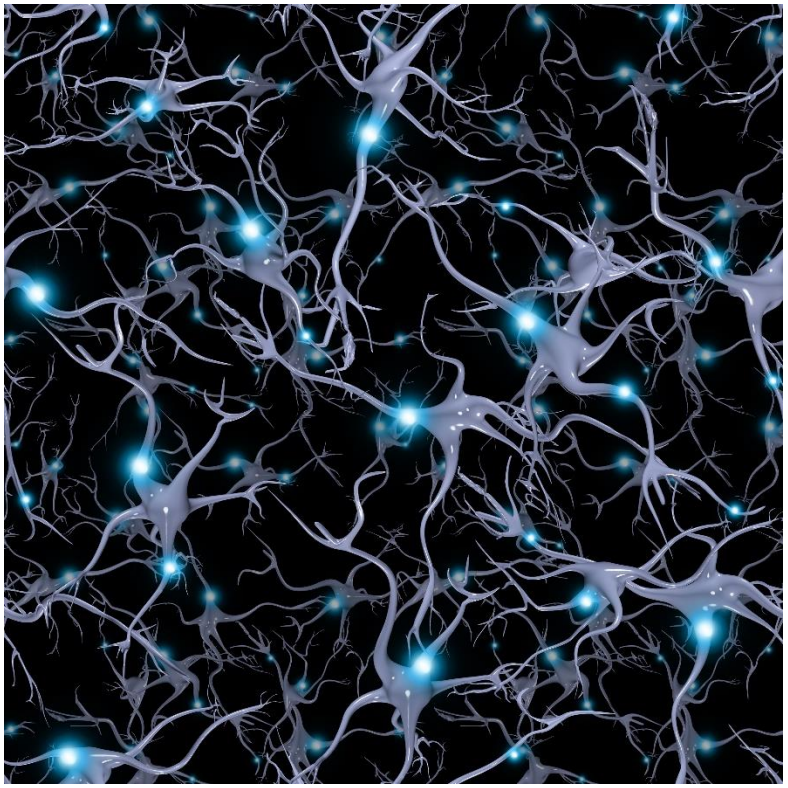
- ETSP Incorporating Dravet Syndrome mouse model
  - Original model developed & made available by the Dravet Syndrome Foundation, Spain (Ana Mingorance) and The Jackson Laboratory
  - ETSP evaluating and optimizing endpoints (hyperthermia-induced seizures; spontaneous recurrent seizures)
- Workshop: "Accelerating the Development of Therapies for Anti-Epileptogenesis & Disease Modification"
  - Outcomes helping guide ETSP's refocused screening efforts to identify treatments for disease prevention & modification

DRAVET SYNDROME FOUNDATION
DELEGACIÓN EN ESPAÑA
www.dravetfoundation.eu



NIH National Institute of Neurological Disorders and Stroke

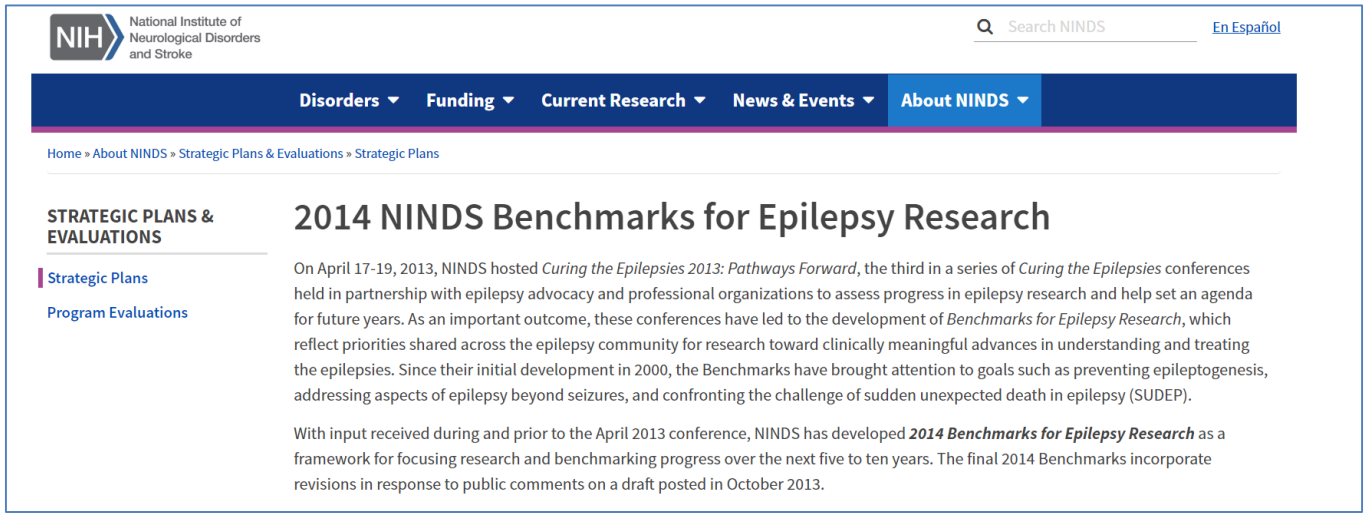
Accelerating the Development of Therapies for Anti-Epileptogenesis and Disease Modification Workshop, August 6-8, 2018



- Working groups presented state-of-science summaries in the areas of clinical studies, industry, preclinical science, and biomarkers and translational science
- Breakout groups discussed gaps and opportunities in research and strategies for overcoming current challenges
- Breakout groups developed set of priorities for research in this area
- The priorities will be the basis of a white paper, currently in progress
- Attendees included researchers, clinicians, representatives from industry, Federal agencies, and patient advocacy/nonprofit organizations

Update to Epilepsy Benchmarks with AES

- 4th Set of Benchmarks **coming soon**
- Curing Epilepsies conference in 2020
  - Agenda under construction with valuable engagement from nonprofit groups
  - AES Epilepsy Research Benchmarks Stewards Committee
  - Co-chairs: Annapurna Poduri (Boston Children's Hospital), Vicky Whittemore (NINDS)



NINDS Nonprofit Forum

Register at https://www.ninds.nih.gov/News-Events/Events-Proceedings/Events/2019-NINDS-Nonprofit-Forum

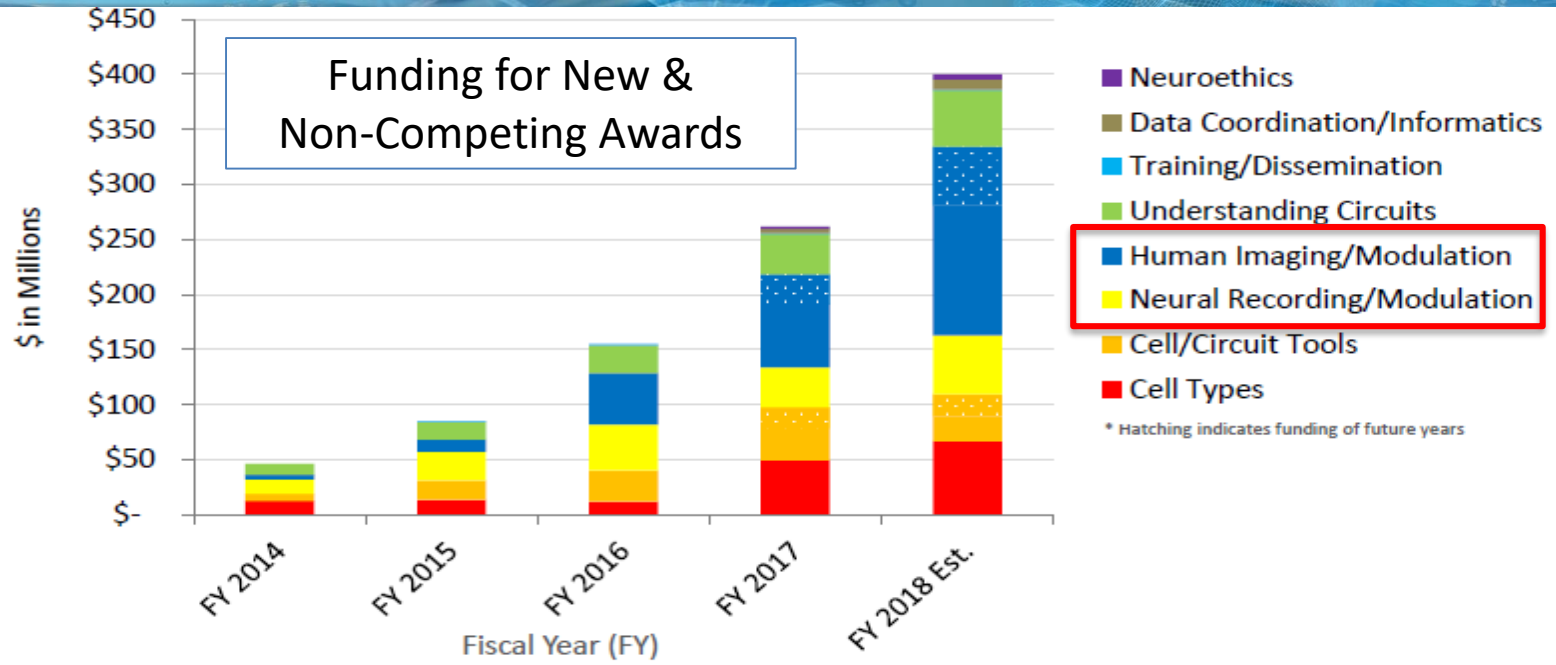
- 12:30 p.m. Tuesday, May 21 to 5:00 p.m. Wednesday, May 22
- Neuroscience Center: 6001 Executive Blvd. Bethesda, MD.

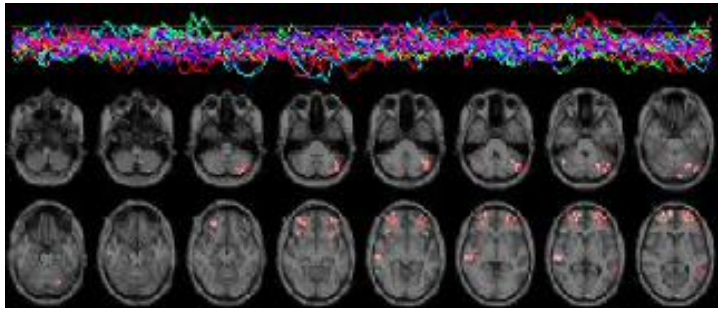
Ongoing Clinical Studies

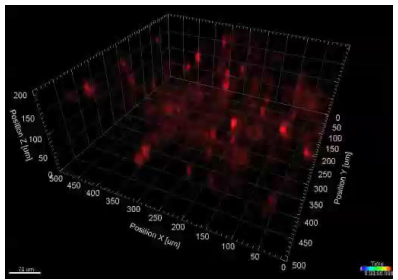
- Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD)
- Consequences of Prolonged Febrile Seizures (FEBSTAT) Study
- Preventing Epilepsy using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREVeNT) Trial

THE BRAIN INITIATIVE®

Focus on Circuit Structure and Function

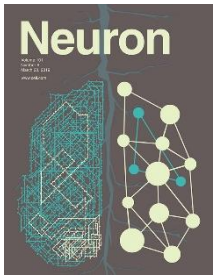


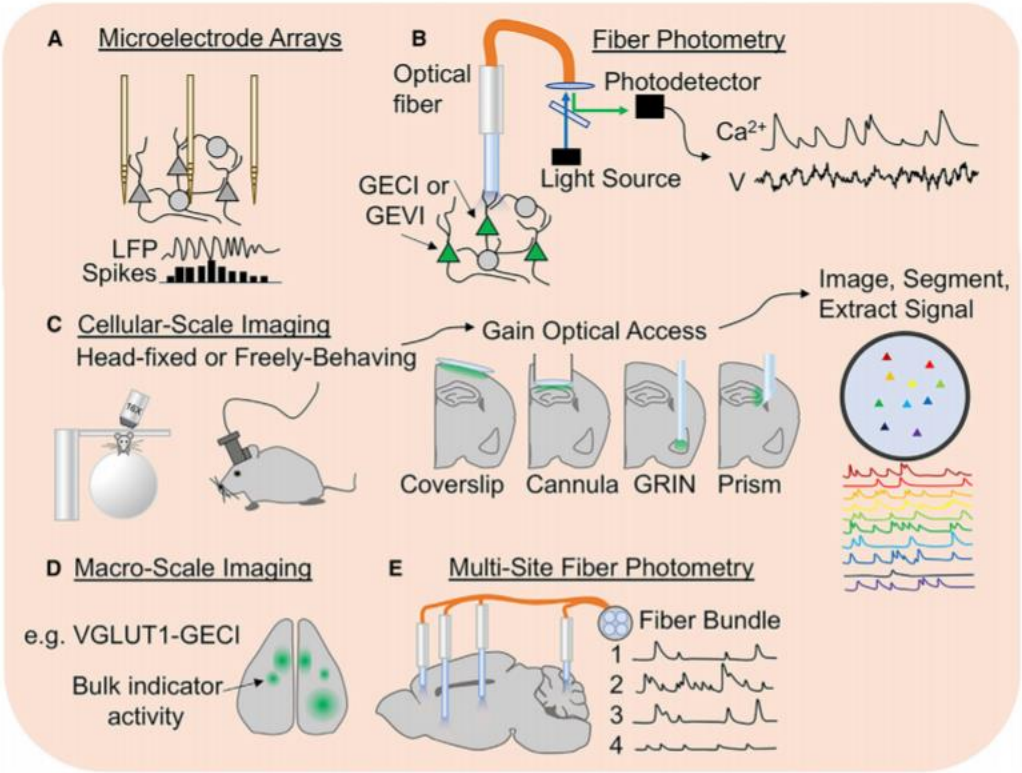




- *Next generation human imaging technologies*
- *Noninvasive neuromodulation*
- *Next generation DBS devices for a range of disorders*
- *Technologies for recording and manipulating neural activity*
- *New optical instruments, electrodes, molecular probes*

Advances in tool development for epilepsy research





Farrell et al, Neuron, 2019

PI: Peter Soltesz

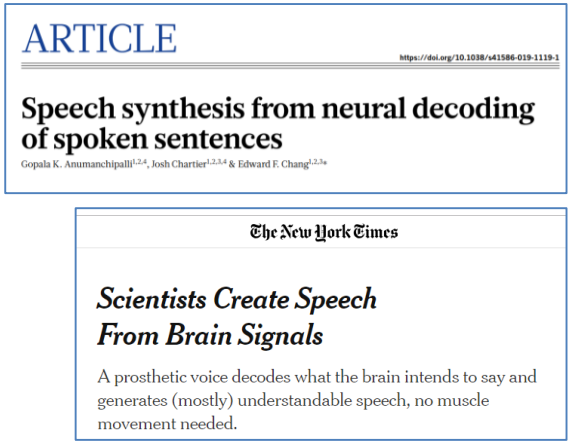
- Epilepsy mutations are present in every cell, but expression can vary brain regions, cell types, and synapses
- Advent of new tools (e.g., optogenetics) is crucial for understanding epilepsy

Epilepsy patients contributing to the BRAIN Initiative

Functional Architecture of Speech Motor Cortex

Edward Chang, University of California, San Francisco

- Developed a neural decoder that leverages kinematic and sound representations encoded in human cortical activity to synthesize audible speech
- Decoder could synthesize speech when a participant silently mimed sentences


ARTICLE

https://doi.org/10.1038/s41586-019-1119-1

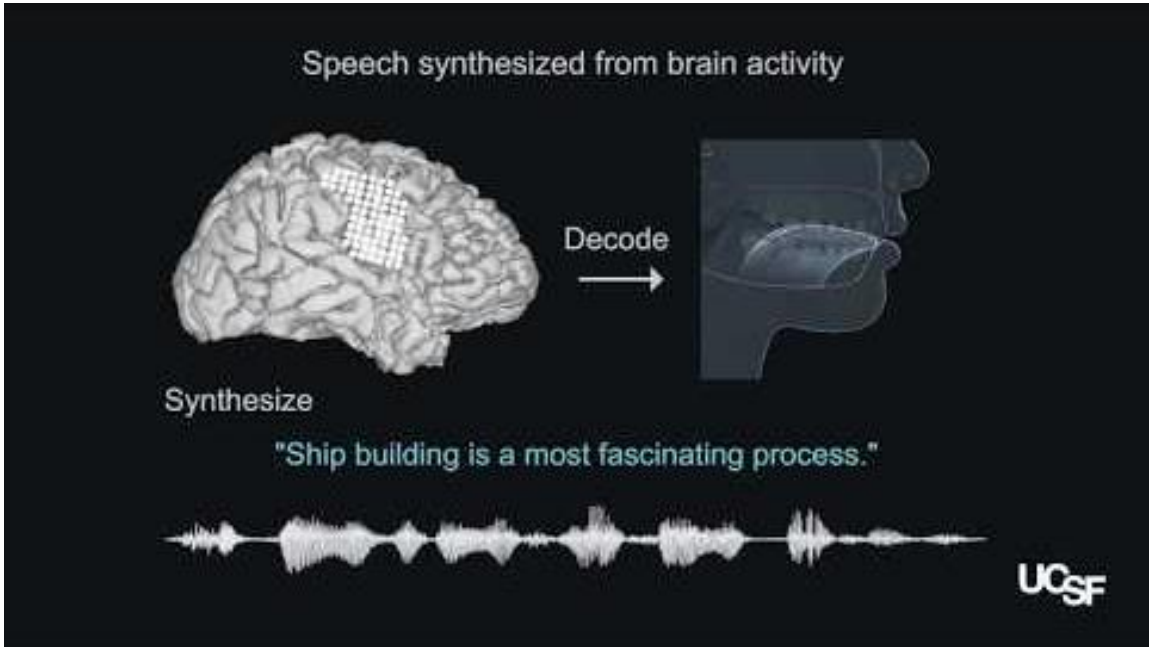
Speech synthesis from neural decoding of spoken sentences

Gopala K. Anumanchipalli[1,2,4], Josh Chartier[1,2,3,4] & Edward F. Chang[1,2,3]*

The New York Times

Scientists Create Speech From Brain Signals

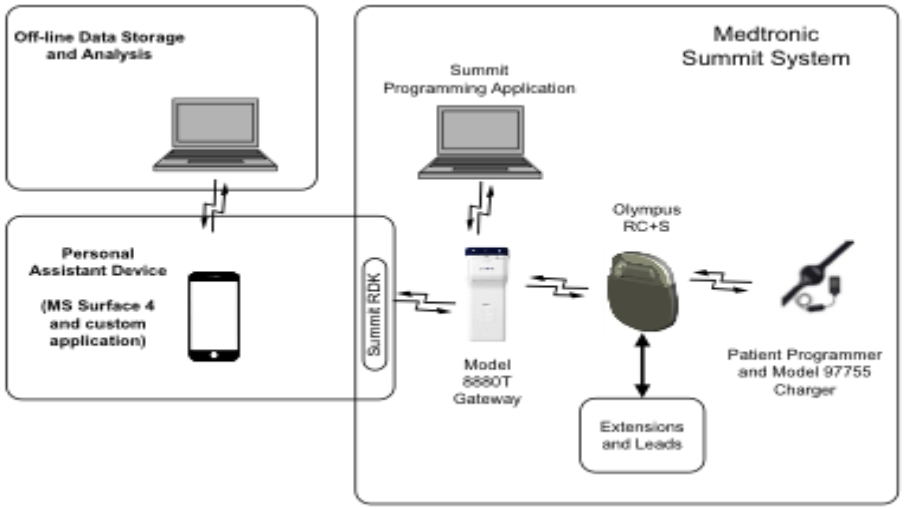
A prosthetic voice decodes what the brain intends to say and generates (mostly) understandable speech, no muscle movement needed.

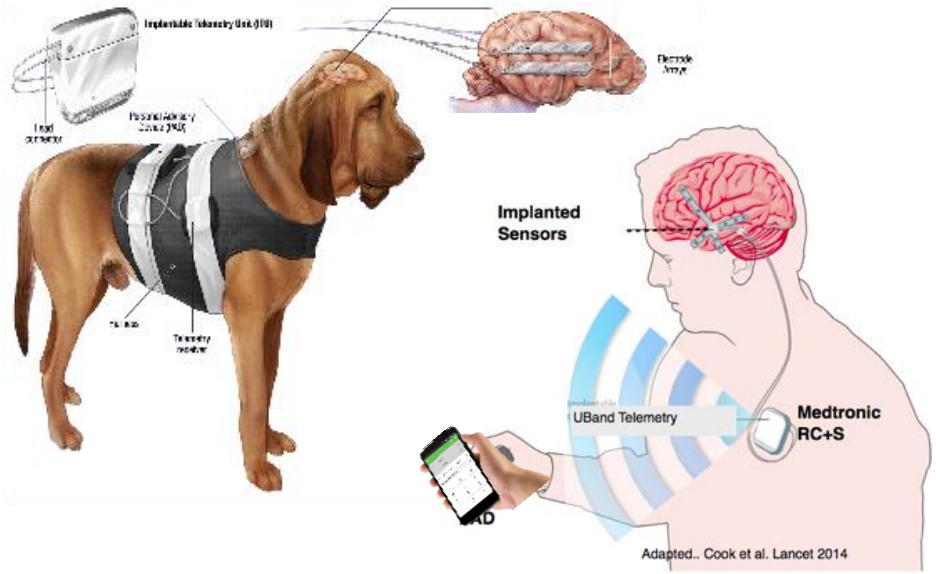


BRAIN: Clinical Efforts

Neurophysiological Brain State Tracking & Modulation in Epilepsy

Goal: *Develop Next Generation Epilepsy Therapeutics Platform based on Medtronic Summit*





New paper!

- "Deep-learning for seizure forecasting in canines with epilepsy"
  - Nejedly et al, J Neur Eng, 2019
- Convolutional neural network (CNN) system to forecast seizures in real time using ambulatory intracranial EEG

National Institutes of Health
Turning Discovery Into Health

Greg Worrell (Mayo Clinic),
NIH UH2NS095495

Scientific Advancements

Ethical considerations demonstrate need for guidelines on continued access to experimental brain implants post-trial for trial participants

- Notable absence of guidelines concerning continued access to experimental brain implants post-trial
- Ethical grounds used to argue that researchers enter into a relationship of trust with patients and thus owe a limited duty of care
- This group highlights necessity of neuroethics in informing responsible human neuroscience research

Lázaro-Muñoz et al., *Nat Rev Neurosci, 2018*

Informing Choice for Neurotechnological Innovation in Pediatric Epilepsy Surgery

- Judy Illes, University of British Columbia
- This project will address the knowledge gap and ethical considerations surrounding novel neurotechnological interventions and the pathway to their adoption for pediatric drug-resistant epilepsy (DRE) in the US and Canada to develop, evaluate and deliver clinician resources for family decision-making, clinician counseling and care.

Thank you!

Walter J. Koroshetz, M.D.

Director

National Institute of Neurological Disorders and Stroke

Email: koroshetzw@ninds.nih.gov

Website: http://www.ninds.nih.gov/

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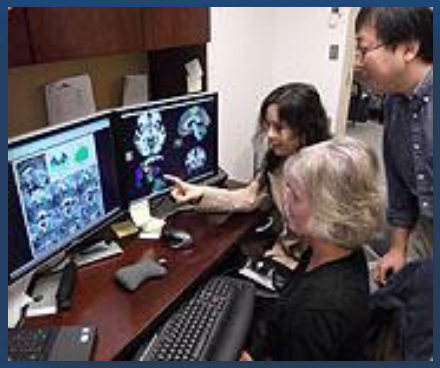

NINDS

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