National Institute of Neurological Disorders and Stroke

Interagency Collaborative to Advance Research on Epilepsy (ICARE): Epilepsy Research at NIH

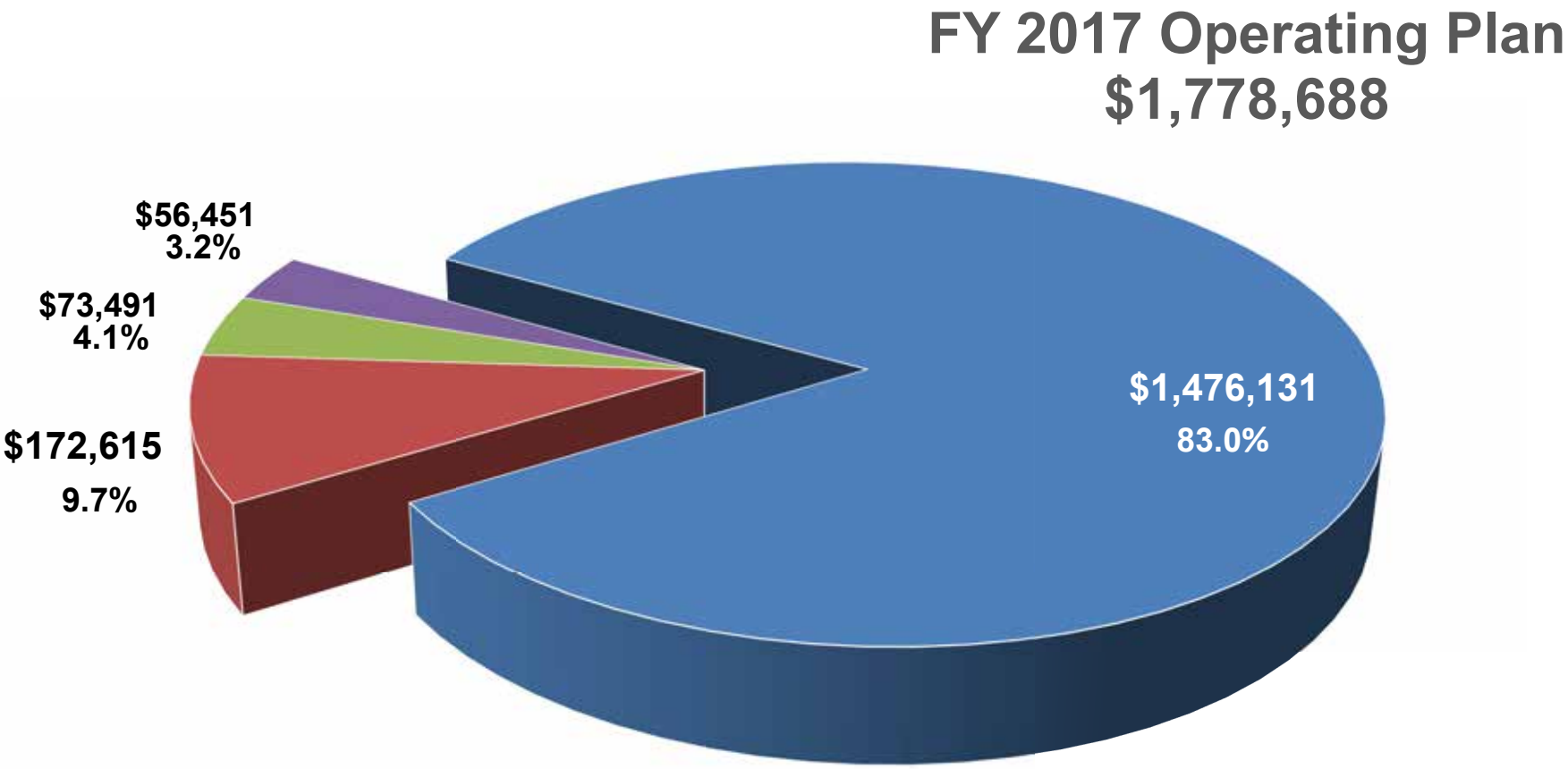
April 12, 2018

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

FY18 Budget Appropriation

- The National Institutes of Health (NIH) received a $3 billion, 8.3% increase to $37 billion.
- The funding provides:
  - $500 million for research related to opioid addiction,
  - $414 million in additional funding for Alzheimer's disease research, and
  - $400 million for the BRAIN Initiative.
- $496 million from the 21st Century Cures Act, which is a full release of the funds and contains specific investment for the BRAIN Initiative and other research efforts.
- A $295 million increase for the National Science Foundation, totaling nearly $7.8 billion

FY 2017 NINDS Appropriation Budget Distribution



Estimated total for epilepsy Research = $161M

NIH National Institute of Neurological Disorders and Stroke

Active Clinical Studies

- Established Status Epilepticus Treatment Trial (ESETT)
- Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) – Supported by NINDS and NICHD
- Consequences of Prolonged Febrile Seizures (FEBSTAT) Study
- Preventing Epilepsy using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREVeNT) Trial

Sudden Death in Young Registry

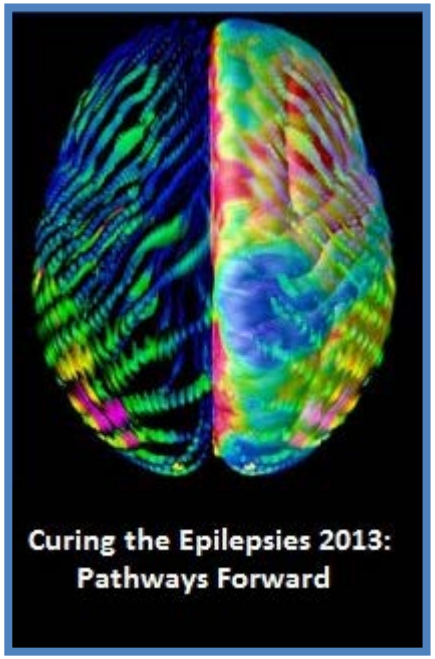
- NINDS continues to partner with NHLBI and the CDC to support the Sudden Death in Young (SDY) Registry
- NINDS has approved continued funding for additional 5 years
- Looking to expand number of states/jurisdictions funded through SDY
- NHLBI and NINDS analyzing data from 2015 and 2016 to determine incidence for Sudden Cardiac Death and SUDEP
- NHLBI-funded investigators will collaborate with Center for SUDEP Research investigators on genetic studies

Epilepsy Centers Without Walls for Collaborative Research in the Epilepsies

- **Epi4K**
  - International effort to analyze DNA from 4,000 people with epilepsy and their relatives to identify disease-causing genes
- **Center for SUDEP Research**
  - Increase our understanding of the mechanisms that lead to SUDEP and find biomarkers to identify those at risk for SUDEP
- **EpiBioS4Rx**
  - Human and animal studies investigating epilepsy that develops after traumatic brain injury

Centers Without Walls for Collaborative Research in the Epilepsies:
Functional Evaluation of Human Genetic Variants (U54)
Review Coming Soon!

Benchmarks for Epilepsy Research: A joint effort between NINDS and AES



I. Understand the causes of the epilepsies and epilepsy-related neurologic, psychiatric, and somatic conditions

II. Prevent epilepsy and its progression

III. Improve treatment options for controlling seizures and epilepsy-related conditions without side effects

IV. Limit or prevent adverse consequences of seizures and their treatment across the lifespan

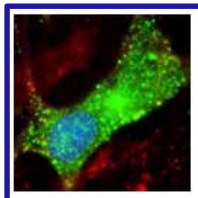
Next Curing the Epilepsies Conference
In 2020!

Recent Advances in Epilepsy Research

Study finds genetic basis for drug response in childhood absence epilepsy

Tuesday, April 11, 2017

NIH-funded research suggests genes may help determine optimal treatments



International study suggests Nodding syndrome caused by response to parasitic protein

Wednesday, February 15, 2017

NIH-funded study also identifies potential new mechanism for some forms of epilepsy

Epilepsy drug discovered in fish model shows promise in small pediatric clinical trial

Friday, February 10, 2017

NIH-funded research suggests zebrafish models may be efficient resource for identifying drugs for clinical use

NIH scientists try to crack the brain's memory codes

Thursday, June 1, 2017

Studies of epilepsy patients uncover clues to how the brain remembers

Science Advances: Common Data Elements for Digital Services in Epilepsy

Accepted: 28 February 2018
DOI: 10.1111/epi.14066

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Common data elements for epilepsy mobile health systems

Daniel M. Goldenholz[1,2] | Robert Moss[3] | David A. Jost[4] | Nathan E. Crone[5] | Gregory Krauss[5] | Rosalind Picard[6,7] | Chiara Caborni[6] | Jose E. Cavazos[8,9] | John Hixson[10] | Tobias Loddenkemper[11] | Tracy Dixon Salazar[12] | Laura Lubbers[13] | Lauren C. Harte-Hargrove[13] | Vicky Whittemore[14] | Jonas Duun-Henriksen[15] | Eric Dolan[16] | Nitish Kasturia[16] | Mark Oberemk[16] | Mark J. Cook[17] | Mark Lehmkuhle[18] | Michael R. Sperling[19] | Patricia O. Shafer[1,4]

TABLE 2 Overall structure of the common data elements

Frequency	Category
Less frequent inserts/updates	Demographics
	Social history
	Other history
	Review of systems
	Seizure history
	Medication side effects
	Past seizure medications
	Diet as treatment
	Mood
	Social support
Frequent inserts/updates	Medication use
	Nonseizure medications
	Supplements/vitamins
	Rescue medications/therapies
	VNS magnet swipes
	Seizure event

VNS, vagal nerve stimulator.
More detail is provided in Appendix S1.

- Significant growth in digital services for people with epilepsy (eg. alerting devices, therapy devices, self-management apps)
- Need for cross-talk between platforms
- CDEs can promote clinical and personal utility for people with epilepsy

Epilepsia. 2018 Mar 31. doi: 10.1111/epi.14066.

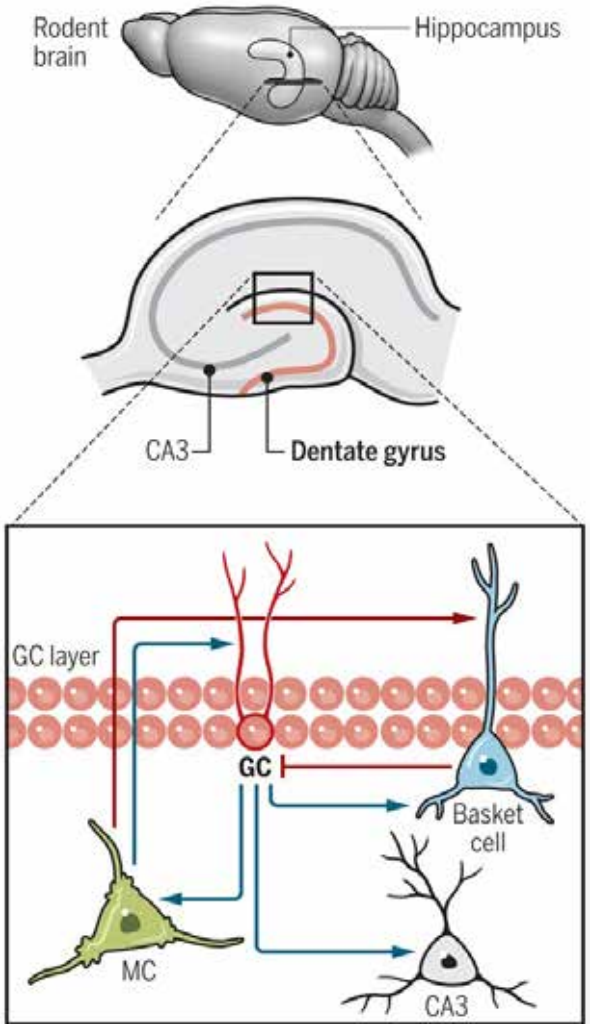
Science Advances: Uncovering the Role of Mossy Cells in Temporal Lobe Epilepsy

NEUROSCIENCE

Dentate gyrus mossy cells control spontaneous convulsive seizures and spatial memory

Anh D. Bui,[1,2]* Theresa M. Nguyen,[1] Charles Limouse,[3] Hannah K. Kim,[1] Gergely G. Szabo,[1] Sylwia Felong,[1] Mattia Maroso,[1] Ivan Soltesz[1]

- Partial loss of mossy cells in dentate gyrus (DG) is a hallmark of temporal lobe epilepsy
- Theory: DG serves as a gated filter for information going to hippocampus
- Optogenetically silencing DG mossy cells impairs spatial memory and terminates seizures in TLE mouse model



Science. 2018 Feb 16;359(6377):787-790.
Science. 2018 Feb 16;359(6377):740-741.

Science Advances: Searching for EEG Biomarkers for Seizure Probability

- How to estimate seizure probability?
- Intracranial EEGs from patients with drug-resistant focal epilepsy with/without cortical stimulation v. patients without seizures (implanted for refractory facial pain)
- Spike rate and amplitude increased in seizure onset zone in patients with epilepsy

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Comparing spiking and slow wave activity from invasive electroencephalography in patients with and without seizures

Brian Nils Lundstrom[a,*], Christian Meisel[b], Jamie Van Gompel[c], Matt Stead[a], Greg Worrell[a]

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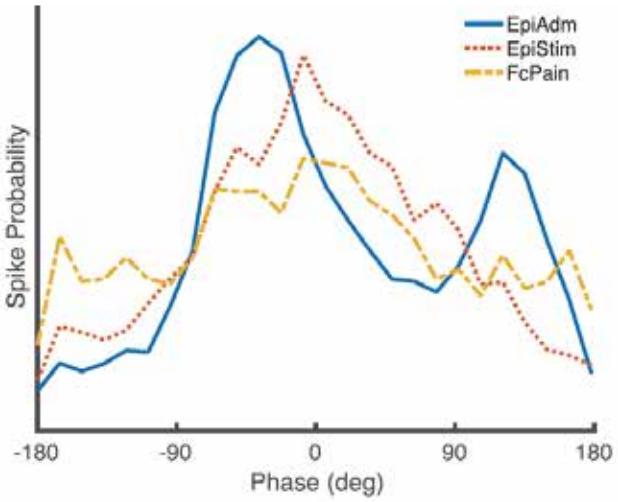
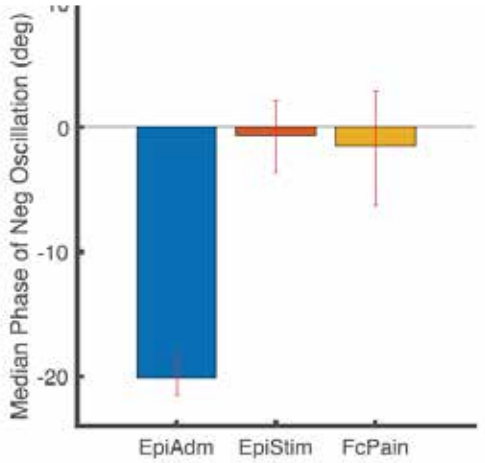
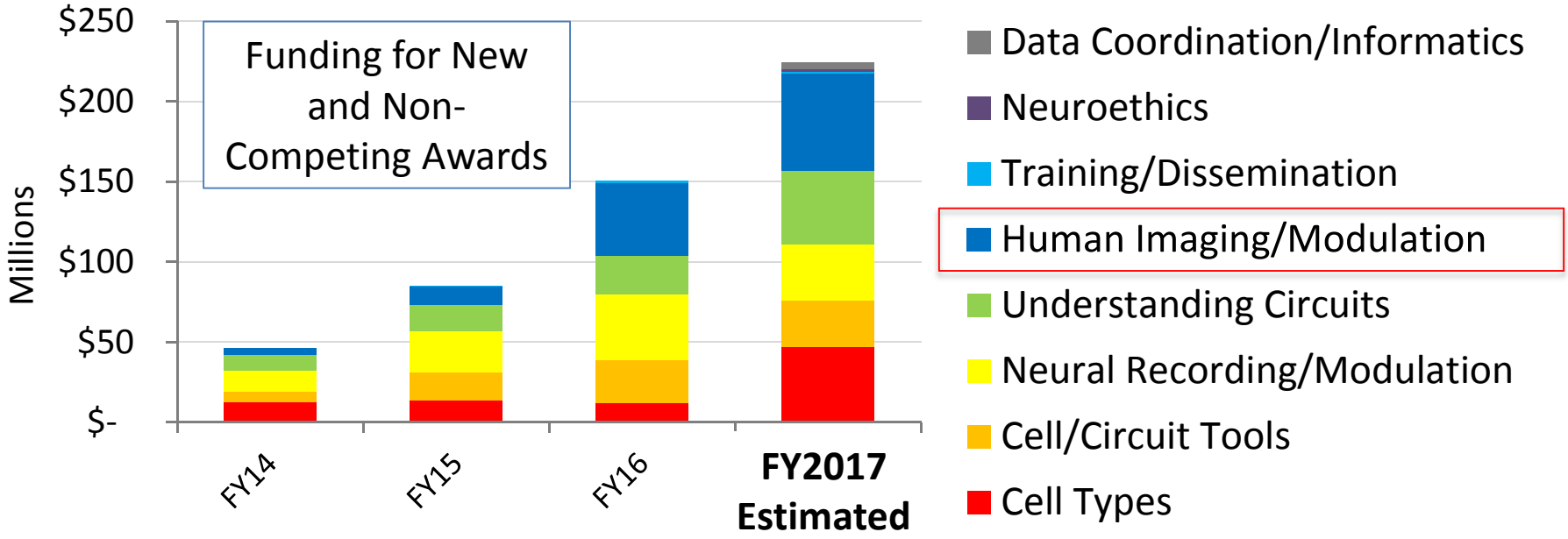
[b] Department of Neurology, University Clinic Carl Gustav Carus, Fetscherstrasse 74, 01307 Dresden, Germany
[c] Department of Neurosurgery, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, USA





Clin Neurophysiol. 2018 May;129(5):909-919

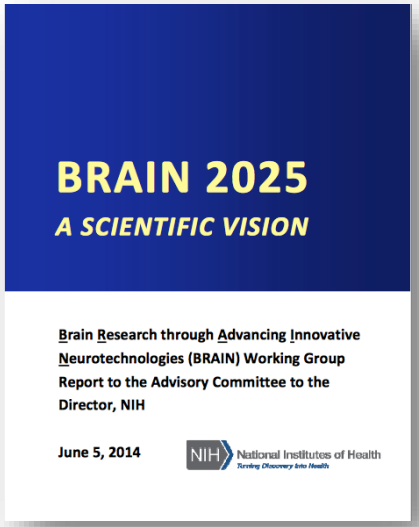
Overall Support for Research Areas



- *Next generation human imaging technologies (phase 2 awards)*
- *Foundations of human imaging*
- *Noninvasive neuromodulation*
- *Next generation DBS devices for a range of disorders*

THE BRAIN INITIATIVE®

Focus on Circuit Structure and Function



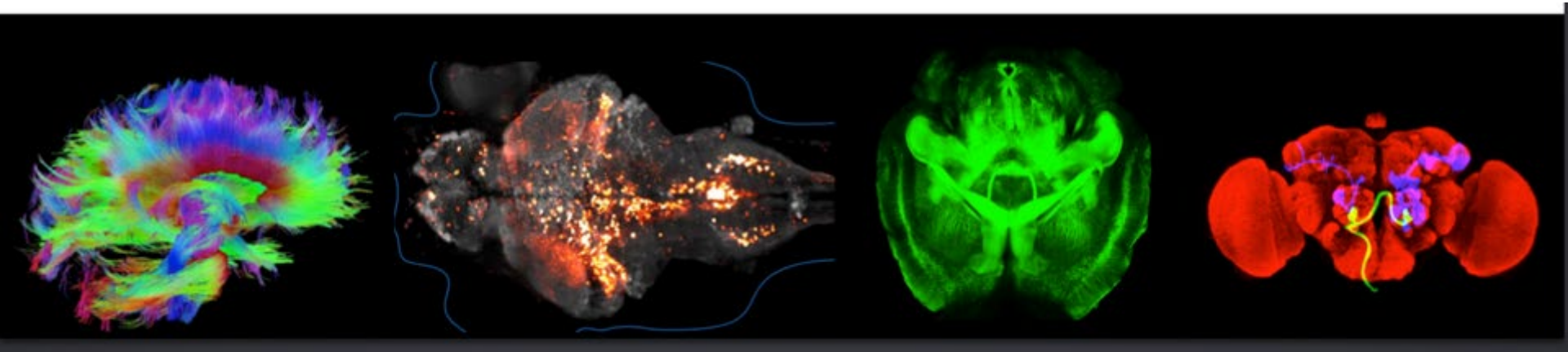
Goal: See the circuits in action to understand:

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

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

FIRST FIVE YEARS — Emphasize technology development

SECOND FIVE YEARS — Emphasize discovery driven science

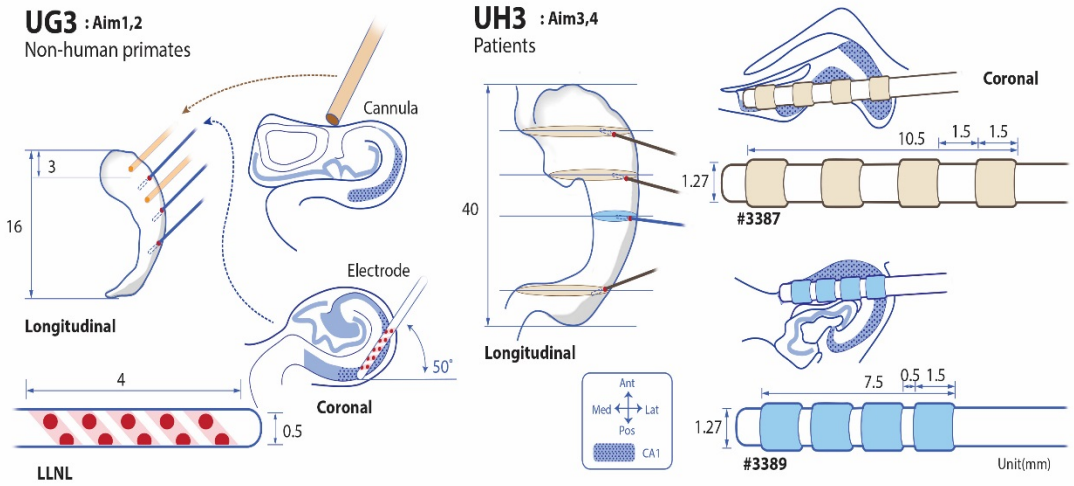


THE BRAIN INITIATIVE®

Asynchronous Distributed Multielectrode Neuromodulation for Epilepsy

PIs: Robert Gross, Annaelle Devergnas, Claire-Anne Gutekunst, Babak Mahmoudi (Emory University), GRANT #1 UG3 NS100559-01

Improve the outcome of drug-resistant epilepsy patients using asynchronous electrical stimulation distributed across a multielectrode array.



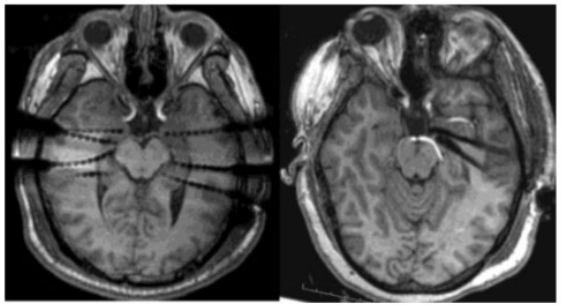


Figure 8: Transverse human implantation of sEEG depth electrodes (left), with 4 multicontact arrays per side (2nd on the right side is out of plane), and 2 RNS (Neuropace) electrodes by same route (right).

NIH National Institutes of Health
Turning Discovery Into Health

BRAIN Initiative Cell Census Network (BICCN)

THE BRAIN INITIATIVE®

NEWS RELEASES

Monday, October 23, 2017

NIH BRAIN Initiative launches cell census

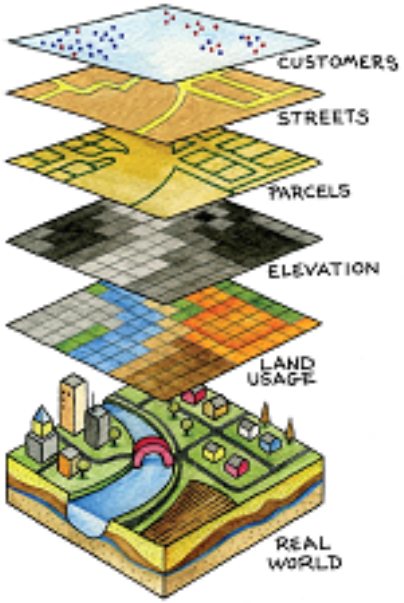
$250 million effort will catalog "parts list" of our most complex organ.

Interoperable Cell Type Brain Atlas

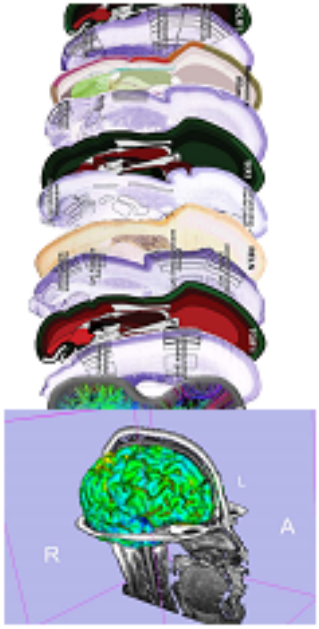
Anticipated outcomes

- Essential knowledge on diverse cell types and their 3D organization
- Open-access 3D digital mouse brain cell reference atlas
- Comprehensive neural circuit diagram in mouse brain

Geographic Information Systems



Brain Cell Census Information Systems



Molecular Signatures (FISH, RNAseq, Immunostaining, etc.)

Anatomy (cell location, size, morphology, cell type composition and ratio, etc.)

Neural Circuits (long distance projections, local circuits, etc.)

Functional Measures (electrophys, calcium imaging, etc.)

Brain cell census data will be mapped to Common Coordinate Systems

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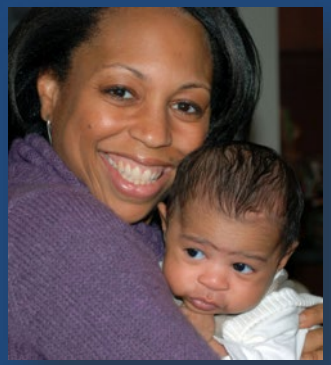
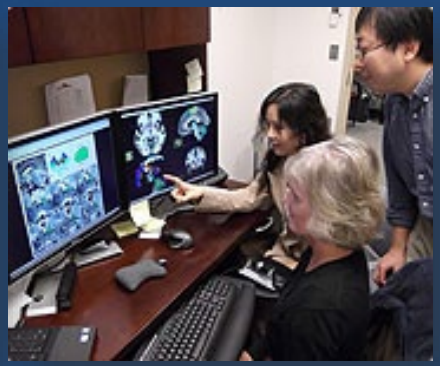
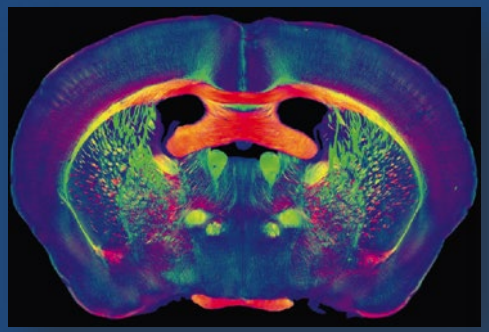
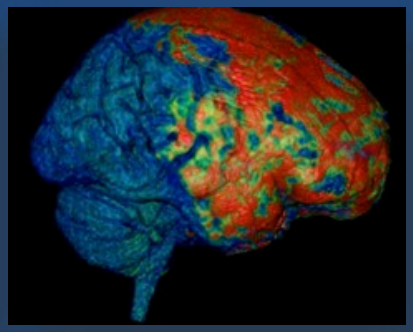
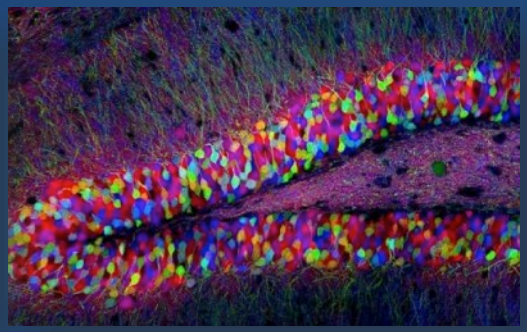
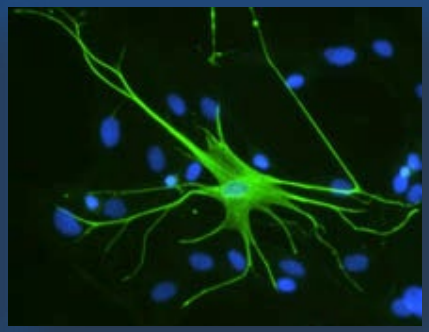



NINDS

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

Thank you!

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