



National Institute of  
Neurological Disorders  
and Stroke

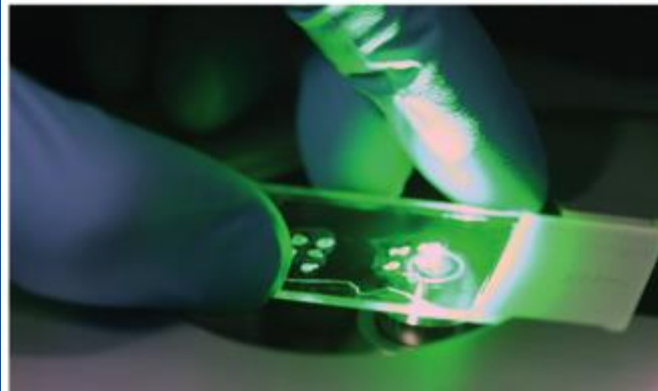
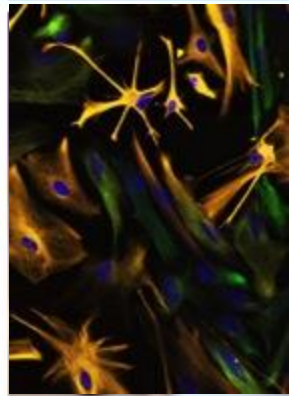
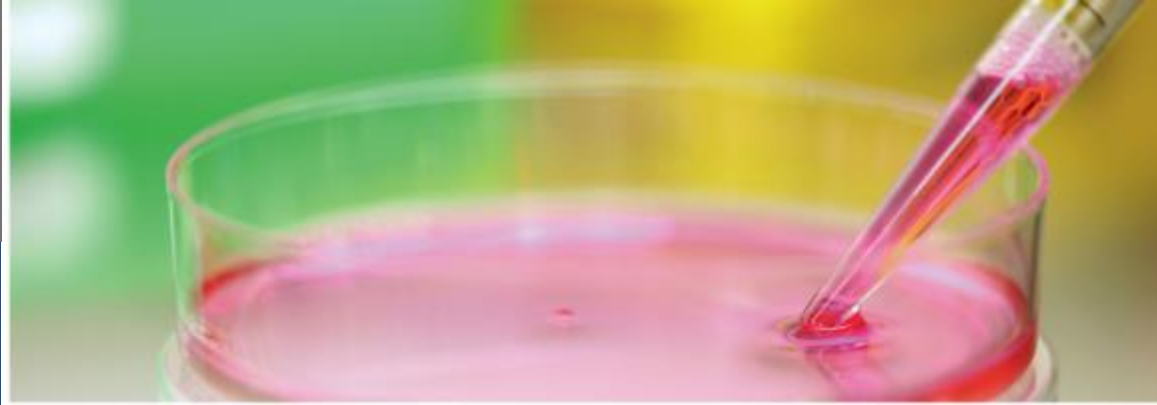
# Special Opportunities for Impactful VA Research: A View from NIH

*Meeting of Research Advisory  
Committee on Gulf War  
Veterans' Illnesses*

November 7, 2016

Walter J. Koroshetz, M.D.

Director, National Institute of  
Neurological Disorders and Stroke, NIH



# 10 things that are hard for NIH to do in clinical research.

- I. Identify long term consequence of studied interventions.
  - I. Grants on average propose to accomplish specific aims in 5 years
- II. Identify the interplay of co-morbidities on outcomes of studied interventions.
- III. Track pre-morbid characteristics and conditions to determine their role in the development of symptomatic disease or response to interventions.
- IV. Recruit a diverse population into studies
- V. Develop a community of research participants and track persons across multiple studies
- VI. Study conditions that are much more common in the military population, ie.,
  - I. Gulf War Illness
  - II. Blast Injury
  - III. Health related consequences of exposures that are uncommon in civilians  
-ie. combat related PTSD
- VII. Health services research such as the VA Quality Enhancement Research Initiative.
- VIII. Study conditions that cross the missions of multiple NIH Institutes/Centers
- IX. Amalgamate data on its myriad of clinical trials in a single accessible database.
- X. Embedding clinical trials into regular medical care such as VA Point of Care Research

# Overview

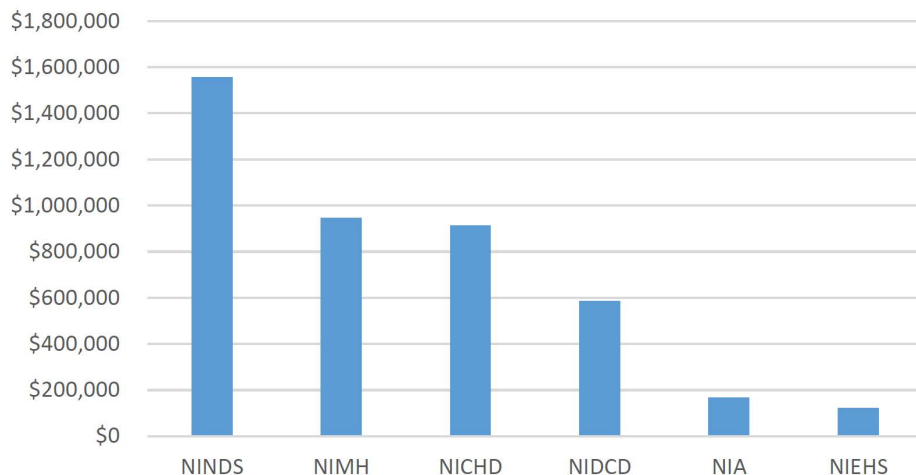
- **NINDS Research of Interest**
  - Chronic Traumatic Encephalopathy (CTE)
  - Concussion
  - Blast injury
  - Chronic Fatigue Syndrome
  - Chronic Pain
- **Interagency Partnerships**
  - NIH-DoD Research on TBI
  - NIH-DoD-VA Partnership in Pain Management
  - VA-NINDS Collaboration for Clinical Trials in PD
- **The BRAIN Initiative**
- **Unique Opportunities for establishing a coordinated system to integrate research and clinical care at the VA**

# National Advisory Neurological Disorders and Stroke Council (NANDSC)

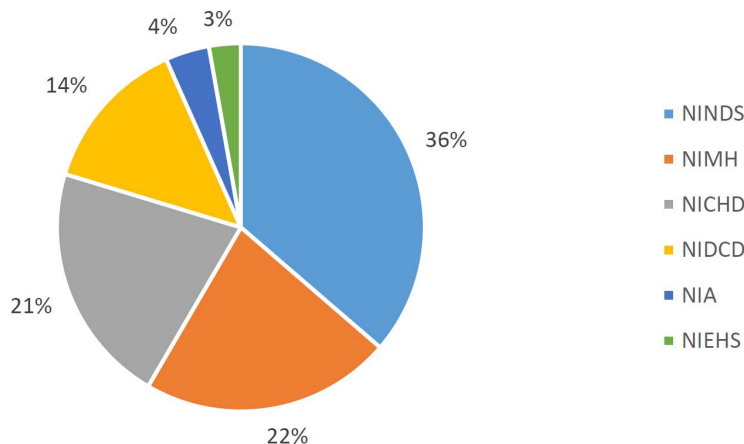
- Each Institute of the National Institutes of Health maintains a National Advisory council which has two general functions:
  - to advise the Institute on policy and procedures affecting the extramural research programs
  - to provide a second level of review for all grant and cooperative agreement applications considered by the Institute for funding.
    - Except for fellowships, the NINDS may not award a grant unless it has been recommended for support by the National Advisory Neurological Disorders and Stroke (NANDS) Council.
- VA Representative: **Christopher Bever, Jr., M.D.**, is a professor in the departments of Neurology and Physical Therapy and Rehabilitation Sciences at the University of Maryland School of Medicine in Baltimore. He is also the Director of the Department of Veterans Affairs (VA) Multiple Sclerosis Center of Excellence, East, and Associate Chief of Staff for Research and Development at the Baltimore VA Maryland Health Care System.
- The NANDS Council meets regularly three times a year: in early February, late May, and mid-September
- Stay up to date:
  - Open session of Council is videocast: <http://videocast.nih.gov/>

# NIH and NINDS-Supported Research on Gulf War

Active NIH Funding on Gulf War



Active NIH Funding on Gulf War



## Actively Funded Investments:

- NIH Funding: \$4.3 Million
- NINDS Funding: \$1.6 Million

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

- Chronic Fatigue Syndrome
- Brain Imaging
- PTSD
- ALS
- Quality of Life
- Lifespan outcome
- Gender and ME/CFS

# Active Gulf War Illness Projects

## Nervous System Development and Plasticity

*Richard Fields, Eunice Kennedy Shriver National Institute of Child Health & Human Development*

- Goal: explore medical implications of **axon communication** with myelinating glia to investigate how myelin may be damaged due to pesticide exposure and in Gulf War Illness
  - Investigate how neurons and glia interact, communicate, and cooperate functionally
  - Determine how different patterns of neural impulses regulate specific genes controlling development and plasticity of the nervous system
  - Determine molecular mechanisms converting short-term memory into long-term memory, and in particular, how gene expression necessary for long-term memory is controlled
- This research resulted in a patent application filed recently for a novel treatment for demyelinating disorders

## Exertional Exhaustion in CFS

*James Baraniuk, Georgetown University*

- Goal: elucidate changes that predict the **transition to exertional exhaustion** in the brain and aberrant response to exercise
  - Developed a novel exercise stress test, fMRI, neurocognitive testing strategy to study this phenomenon in GWI subjects who met 1994 CFS criteria
- Protocol identified novel finding of significantly increased axial diffusivity in specific white matter tracts by diffusion tensor imaging (DTI) that was predictive of GWI status compared to controls
- Exercise perturbs neurophysiological brain networks that led to 2 GWI phenotypes that were associated with exercise induced changes in autonomic control, white matter integrity, cortical and brainstem atrophy, and brain blood flow dynamics.

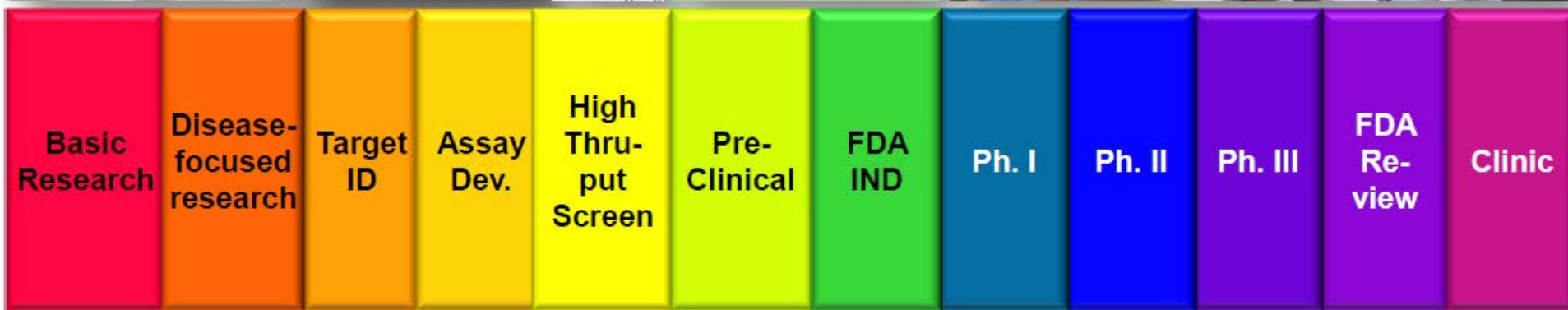
# Active Gulf War Illness Projects

## Lead and Other Neurotoxins as Risk Factors for Amyotrophic Lateral Sclerosis

*Dale Sandler, National Institute of Environmental Health Sciences*

- Goal: This study evaluated the association of **BMI and BMI change** at different ages with ALS risk using GENEVA (Genes and Environment in Veterans with ALS) data. It also examined associations of ALS with **blood levels of selenium (Se), zinc (Zn), copper (Cu), and manganese (Mn)**.
  - ALS was positively associated with exposure to herbicides for military purposes, nasopharyngeal radium, exhaust from heaters or generators, high-intensity radar waves, explosions within one mile, herbicides in the field, mixing and application of burning agents, burning agents in the field, and Agent Orange in the field.
  - Compared to a moderate increase in BMI between age 25 and 40, stable or decreasing BMI was associated with a 60% increase in ALS risk.
  - Suggests deficiencies of Se and Zn and excess Cu may have a role in ALS etiology.
- This research corroborates that elevated blood lead is associated with increased ALS risk and suggests that increased bone turnover in ALS cases does not fully explain this association.

# NINDS Is Investing Across the Research Spectrum





# EValuation Of Longitudinal outcomes in mild TBI Active Duty Military and Veterans The EVOLVE study

PI: Christine Mac Donald, PhD, University of Washington Seattle, WA

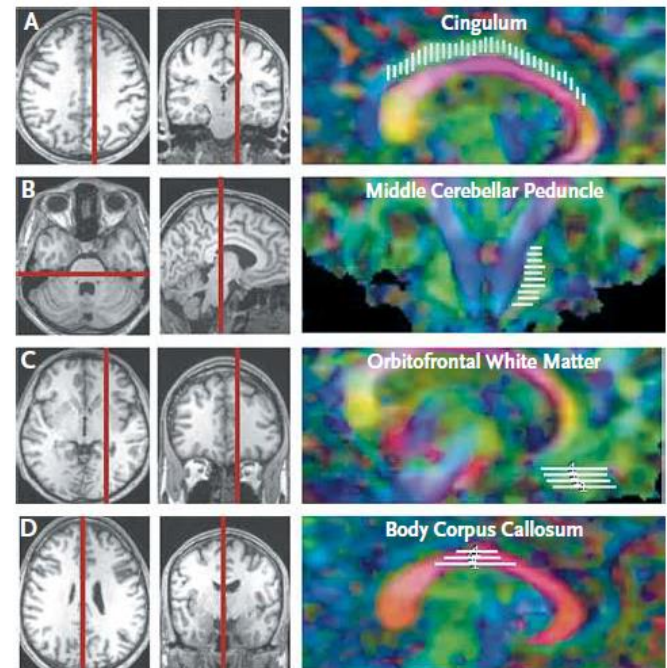
- **Premise:** 5-7 year follow up of all 591 Service Members 54% mild TBI, 46% combat-deployed control previously enrolled in Landstuhl, Germany and Kandahar, Afghanistan
  - Dr. Mac Donald lived and worked at Landstuhl from 2008-2013 to complete the early studies and has seen these patients from the point of injury now out to 5-7 year follow providing unprecedented information about trajectory over time not just with injury recovery but through service separation to appreciate impact on changes in clinical care services.
- **Funding:** NIH RO1 - NINDS
- **Goal:** Leverage early clinical and imaging data from point of injury and one-year follow up to develop complex predictive models of long term outcome.



## Detection of Blast-Related Traumatic Brain Injury in U.S. Military Personnel

Christine L. Mac Donald, Ph.D., Ann M. Johnson, Dana Cooper, B.S., Elliot C. Nelson, M.D.,  
Nicole J. Werner, Ph.D., Joshua S. Shimony, M.D., Ph.D., Abraham Z. Snyder, M.D., Ph.D., Marcus E. Raichle, M.D.,  
John R. Witherow, M.D.,\* Raymond Fang, M.D., Stephen F. Flaherty, M.D., and David L. Brody, M.D., Ph.D.

<http://www.nejm.org/doi/full/10.1056/NEJMoa1008069>



# Astroglial Scarring After Blast Exposure

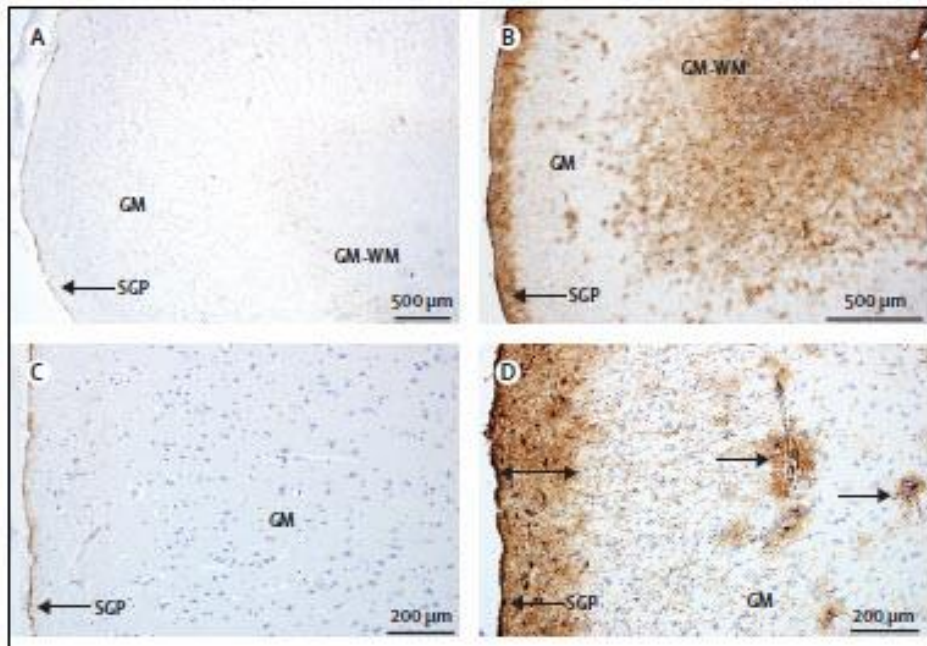


## Characterisation of interface astroglial scarring in the human brain after blast exposure: a post-mortem case series

Sharon Baughman Shively\*, Iren Horkayne-Szakaly\*, Robert V Jones, James P Kelly, Regina C Armstrong, Daniel P Perl

Control

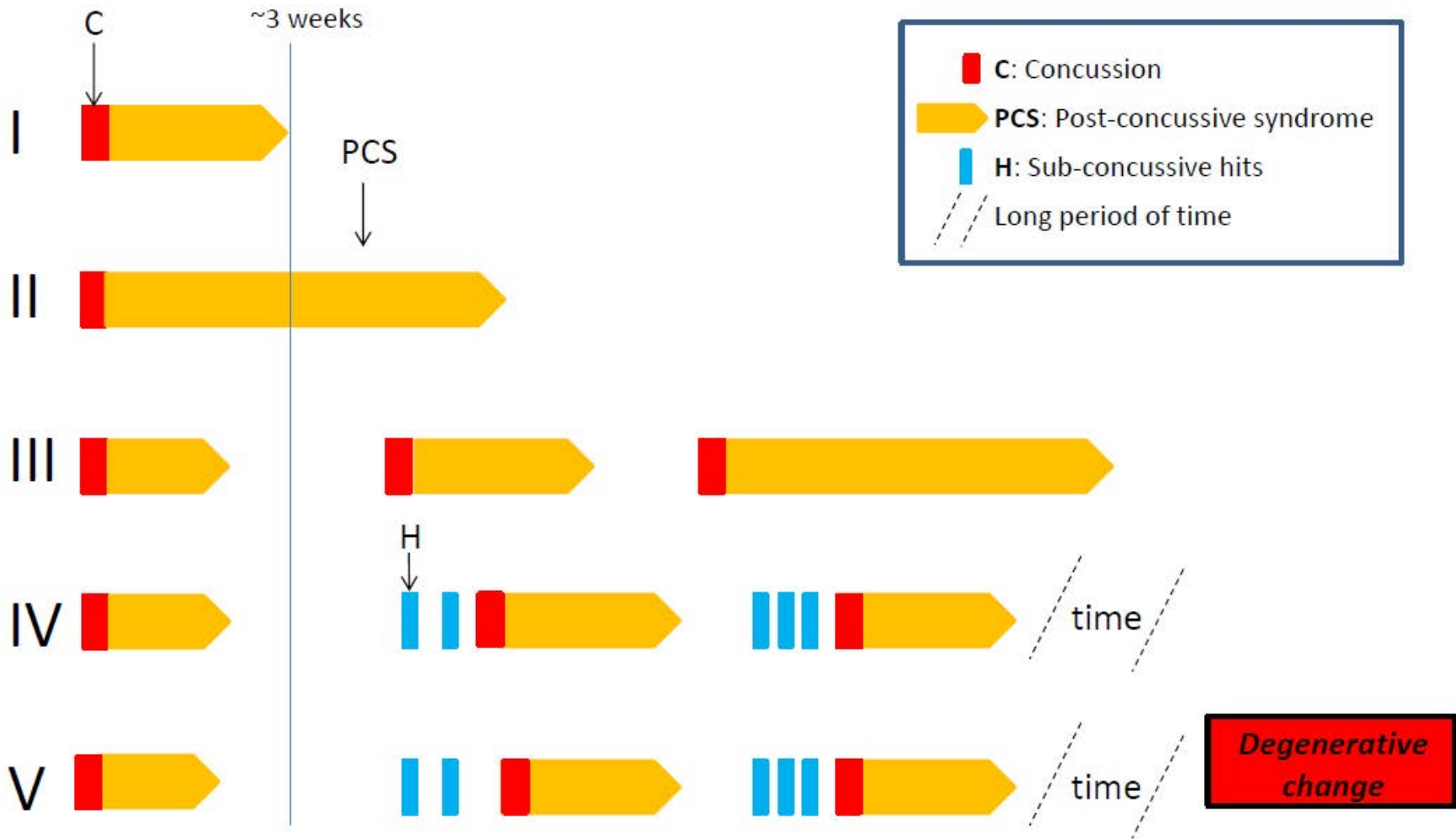
Chronic Blast TBI



*Lancet Neurology*, vol. 15, 2016

- Post-mortem study of personnel that sustained blast exposure (chronic vs acute).
- **Chronic blast exposure cases showed severe astroglial scarring in tissues adjacent to CSF, penetrating cortical blood vessels, and grey-white matter junctions.**
- Less extensive, but prominent, astrogliosis was observed in the same brain regions of acute blast TBI cases.
- Hypothesis: blast wave damages structural boundaries between tissues of different densities.

# Concussion: Scope of the Issue



# Concussion Assessment, Research and Education (CARE): A large-scale, multi-site study of the natural history of concussion in both sexes and multiple sports



**NCAA•DOD**  
Grand Alliance  
CARE Consortium

**The proposed three-year study marks what is considered to be the most comprehensive investigation of sport-related concussion conducted to date. This study will facilitate a better understanding the natural history and neurobiology of concussion in athletes.**

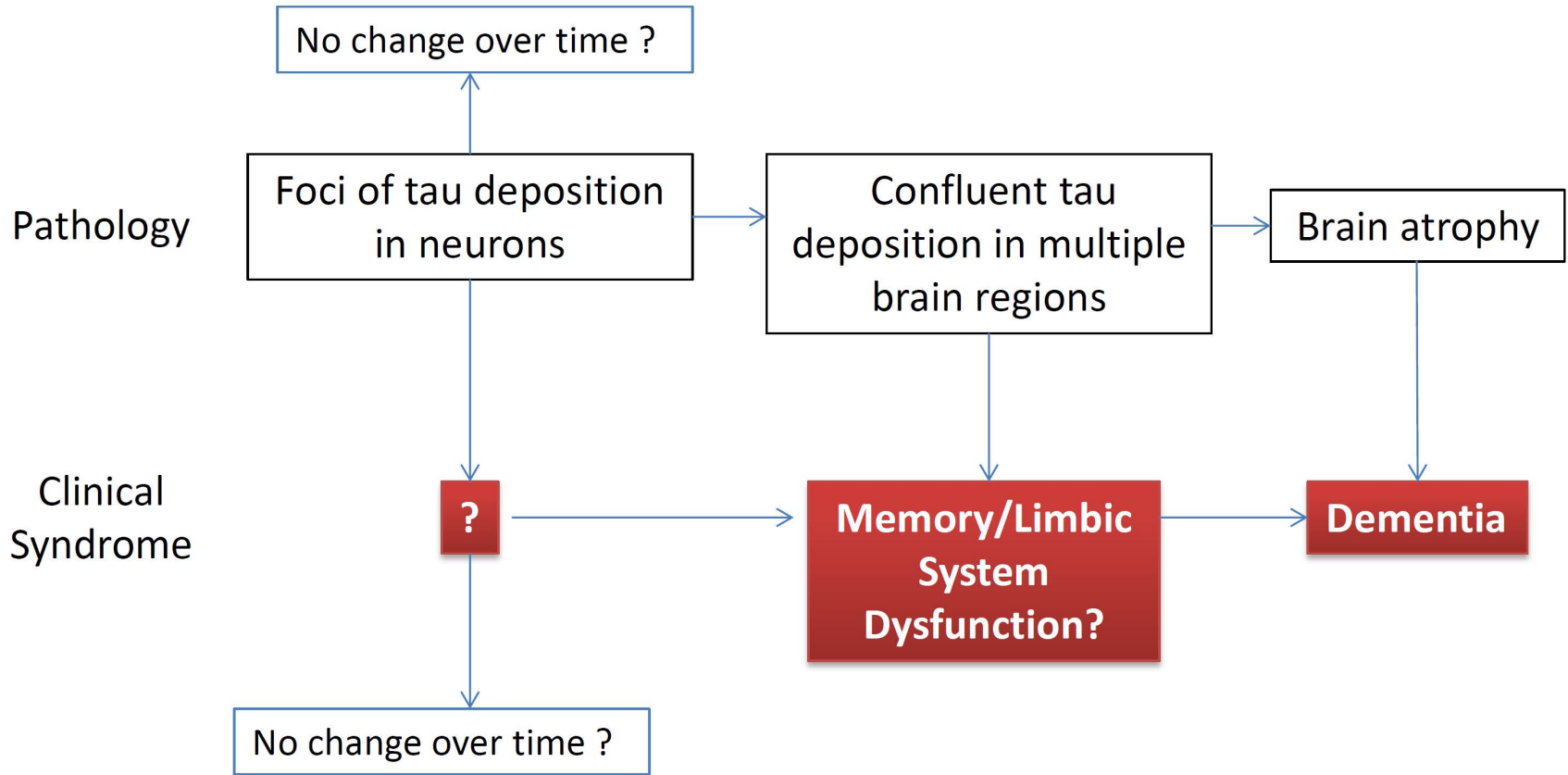
- West Point and Air Force will be conducting a partial-Advanced Research Core, or “pARC,” at their sites that include all aspects of the ARC protocol with the exception of imaging.
- In addition to the ARC sports of basketball, football, ice hockey, and soccer, the service academies will also include rugby, wrestling, boxing, and combat training injuries.

# 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 neurodegeneration*)?
5. Given similar exposures, how can we **predict** an individual's risk for CTE? (*e.g., genetics, environmental influences, lifestyle, etc.*)

*Degenerative  
change*

# Chronic Traumatic Encephalopathy (CTE)



**DECADES**

1960's

1970's

1980's

1990's

2000's



# Defense and Veterans Brain Injury Center

The TBI operational component of the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) since 1992

- Treats, supports, trains and monitors service members, veterans, family members and providers who have been, or care for those who are, affected by TBI
- 16 sites at Military Medical Centers and Veterans Affairs Hospitals (1 in Landstuhl, Germany)
- Walter Reed-Bethesda offers regional Education Outreach and Care Coordination
  - Actively recruiting for 10 IRB-approved protocols:



Louis French  
DVBIC Site Director, Walter Reed

- Exploring the Natural History of TBI within a Military Cohort: a Longitudinal Database & Blood Banking Study
- Military Blast-related TBI: A Study of Neuroanatomical and Neurobehavioral Sequelae and Low Cost Clinical Preventions
- Prospective Traumatic Brain Injury Tracking Protocol
- An fMRI study of TBI Associated with Blast Injury
- A Randomized Controlled Pilot Study of the Effectiveness and Feasibility of Novel Rehabilitation approaches for OIF and OEF patients with Persistent Complaints of Cognitive Dysfunction following TBI

<http://dvbic.dcoe.mil/location/walter-reed-nmmc-md>



# Center for Neuroscience and Regenerative Medicine Brain Tissue Repository

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

The **CNRM Brain Tissue Repository** offers scientists the opportunity to advance TBI research by comparing injured and uninjured brain tissue

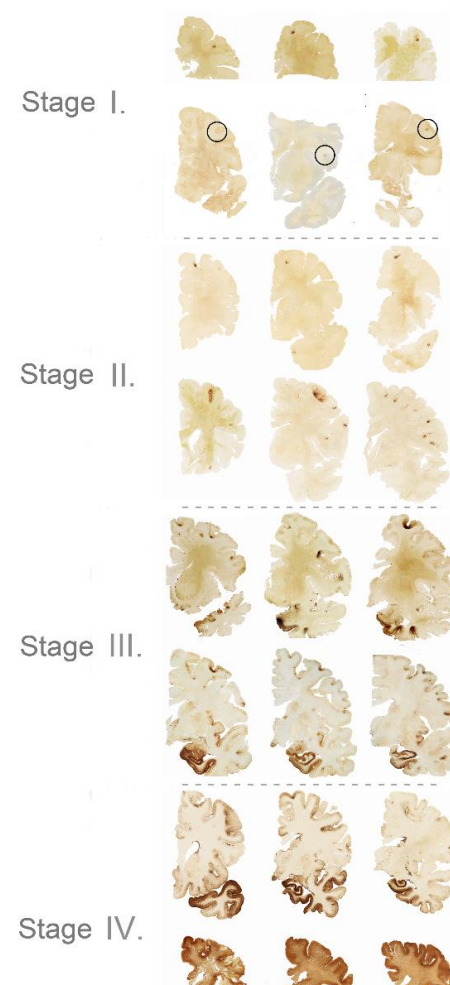
- The goal is to better understand TBI and how to care for military personnel after head injury
- Donations include service members and civilians with or without history of TBI
- The need for research has increased as ~ 15-20% of service members returning from Operation Iraqi Freedom report having TBI during tours of duty
- Research is conducted by the Department of Defense and TBI researchers throughout the country



# Is CTE more common than previously considered? In Veterans? In suicide?

- 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.

The Stages of CTE



National Posttraumatic Stress Disorder Brain Bank

Department of Veterans Affairs Biorepository Brain Bank



VA Secretary joins others in pledge to donate their brains to VA-lead TBI research program

# ARMY STARRS

## *Army Study to Assess Risk and Resilience in Servicemembers*

A partnership between U.S. Army and the National Institute of Mental Health (NIMH) to assess suicide prevention in military personnel

- Study ran from 2009-2014
- Largest study of mental health and resilience ever conducted among military personnel
- Included data from 72,000 Soldiers from more than 75 different locations in the U.S. and around the globe
- 5 primary components:
  - Historical Administrative Data Study
  - All Army Study
  - New Soldier Study
  - Soldier Health Outcomes Study
  - Pre/Post Deployment Study

# ARMY STARRS-LS

*Army Study to Assess Risk and Resilience in Servicemembers – Longitudinal Study*



- Funded by Department of Defense
- Continuation of ARMY STARRS research study
- Study runs from 2015 – 2020
- Purpose: to create practical, actionable information on risk reduction & resilience-building for suicide, suicide-related behavior, & other mental/behavioral health issues in military
- Goals:
  - Extend the reach of ARMY STARRS by conducting longitudinal follow-up studies of Soldiers throughout their Army careers and their transition to civilian life
  - Continue use of ARMY STARRS data and infrastructure
  - Collect additional data for ARMY STARRS participants
  - Further use of ARMY STARRS data for analysis



# Patient Protection and Affordable Care Act 2010

## Section 4305: Advancing Research and Treatment for Pain Care Management

Secretary HHS to convene an

**IOM Conference on Pain** to recognize pain as a significant public health problem, evaluate care, identify barriers to care, and establish action plans to reduce barriers and improve pain research, education, and care.

Secretary HHS to establish the

**Interagency Pain Research Coordinating Committee** to coordinate all efforts across Federal agencies and other departments that support research related to pain.

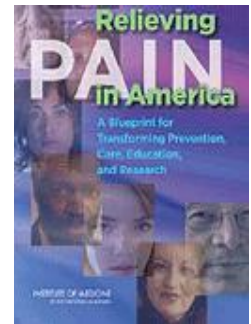


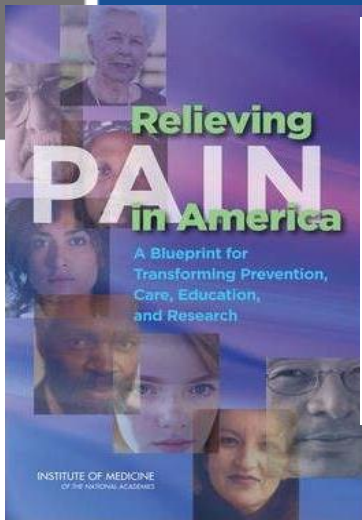
*The*

## Interagency Pain Research Coordinating Committee

**VA Representative:**

**Audrey Kusiak, PhD** is a Portfolio Manager in the Rehabilitation Research and Development Service at the Department of Veterans Affairs, Office of Research and Development, where her portfolio includes research on spinal cord injury, pain, regenerative medicine and translational neural repair.





***IOM's Core Recommendation:*** “The Secretary HHS should 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.”



# National Pain Strategy

**A Comprehensive Population Health Level Strategy for Pain**

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





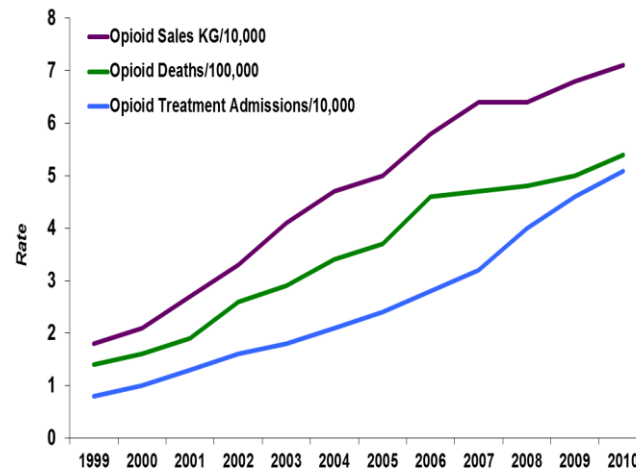
National Institutes  
of Health

## 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 treatment.
- ❖ 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.

# NIH-DoD-VA Partnership in Pain Management

- The National Advisory Council on Complementary and Integrative Health (NACCIH) partnered with the Department of Defense (DoD) and the Department of Veteran Affairs (VA) to seek advise for the development of a pain management initiative to examine Veterans' health



- **NIH-DoD-VA Pain Management Collaboratory Initiative**

Draft Funding Opportunity Announcements:

- NIH-DoD-VA Health Care Systems Research Collaboratory on Non-Pharmacological Approaches to Pain Management and Comorbidities in U.S. Military Personnel, Veterans, and Their Families - Pragmatic Clinical Trials Demonstration Projects (UH2/UH3)
- NIH-DoD-VA Pain Management Collaboratory - Coordinating Center (U54)

Currently finalizing which agencies (VA, DoD) and NIH institutes, centers, and offices (NIH ICOs) plan on participating in this initiative

# Clinical Trials Involving Veterans

- Actively recruiting clinical trials from National Center of Complementary and Integrative Health (NCCIH):
  - **Pain Management Using Mobile Technology in Veterans with PTSD and TBI** ([NCT02237885](#))
    - **Purpose:** Test the effectiveness of using mobile neurofeedback devices for reducing pain symptoms in veterans with PTSD and TBI
    - **Outcome Measures:** Number of ten minute neurofeedback sessions completed; Change in self reported pain score
  - **Improving Opioid Safety in Veterans using Collaborative Care and Decision Support (OPTI)** ([NCT02230722](#))
    - **Purpose:** Encourage non-opioid pain management by developing a collaborative care intervention using attention control and motivational interviewing
    - **Outcome Measures:** Greater self-efficacy in pain management; satisfaction level in pain-related care
  - **Bright Light Treatment at home to Manage Chronic Pain in U.S. Veterans** ([NCT02373189](#))
    - **Purpose:** Develop a self-administered morning bright light treatment to manage chronic pain and improve PTSD symptoms
    - **Outcome Measures:** Pain intensity; Pain sensitivity



# Pilot: Health Care Systems Research Collaboratory

## Pragmatic Trial



**NPS Objectives:** development of surveillance and evaluation information systems to query national level surveys and refine and employ electronic health care databases to characterize the nature and impact of chronic pain and treatment gaps.

**Researchers from integrated health care delivery systems Kaiser NW, Group Health, Veterans Health will address NPS Objectives**

- estimate prevalence of chronic and high impact chronic pain in primary care and among those with anatomically defined pain conditions
- employ standardized EHR data methods to determine the extent to which people with pain receive treatments and services, the extent of use of treatments that evidence has shown are effective and underused - or ineffective and overused
- refine and utilize metrics for tracking changes in pain-related parameters and identify emerging needs, including enhanced self-management support for chronic pain

## A Veteran with Phantom Limb Pain

*Main Menu:* Watch the video to learn what this case study will cover and how to navigate through the module. Then click on any of the buttons to begin the course.

Case  
Study:  
Peter  
James



Learning  
Resources

Additional  
Reading

Testing Center





## Defining high-impact chronic pain

### 2016-2017 NHIS pain questions

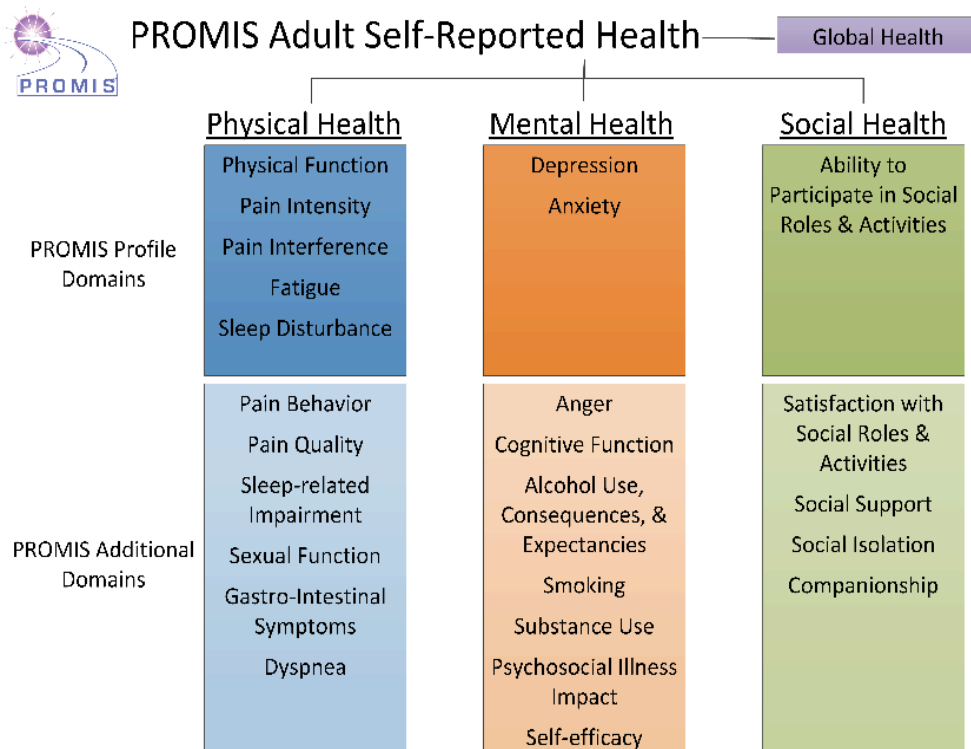
- 1. In the past six months, how often did you have pain?**  
Never Some days **Most days** **Every day**  
[concept: chronic vs non-chronic pain]
- 2. Over the past six months, how often did pain limit your life or work activities?**  
Never Some days **Most days** **Every day**  
[concept: low and high impact pain]

# Pain Assessment Screening Tool and Outcomes Registry (PASTOR)

## NIH Patient Reported Outcome Measures: Tool Development and Validation

### Adult Assessment

PROMIS developed self-report measures for adults for the functions, symptoms, behaviors, and feelings shown here. Measures are applicable to the general population and to those with chronic conditions.

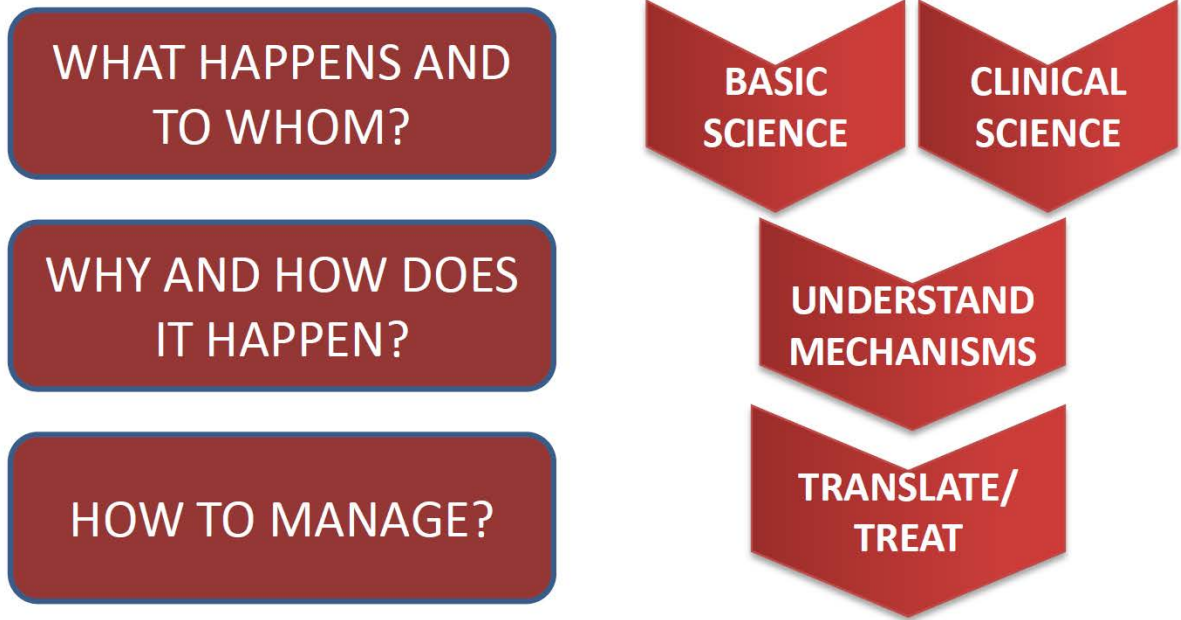
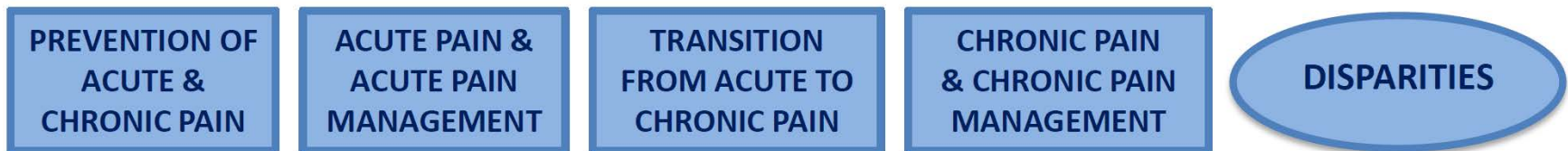


Customized for servicemembers

The top banner features the logo of the Defense & Veterans Center for Integrative Pain Management, which includes a silhouette of a human figure with a sword and a caduceus. Below the banner is a screenshot of the PASTOR Clinician Report, showing various data points, graphs, and tables related to patient assessment and outcomes.

# National Pain Research Strategy

**Focus on the Continuum of Pain:** pain as a temporal process, beginning with an acute phase that may progress to a chronic maladaptive state



# All of Us<sup>SM</sup>: *The Precision Medicine Initiative*<sup>®</sup> Cohort Program

- **MISSION:** To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care



- Cohort program is cornerstone of the larger PMI – led by the NIH
- One million or more volunteers, reflecting the broad diversity of the U.S.
- Opportunities for volunteers to provide data on an ongoing basis
- Launch to happen in phases with an estimated 3–4 years to reach one million
- Data shared freely and fast to inform a variety of research studies
- Participants will be true partners—not patients, not subjects—in the research process

**All of Us**<sup>SM</sup> | The Precision Medicine Initiative<sup>®</sup>  
THE FUTURE OF HEALTH BEGINS WITH YOU



# VA and Precision Medicine Initiative® Partnership

**Million Veteran Program (MVP):** In partnership with the Precision Medicine Initiative, MVP's goal is to establish a national, voluntary research study of genetic, military exposure, lifestyle, and health information on Veterans to improve health and quality of life.



## Million Veteran Program (MVP)

MVP is a national, **voluntary** research program funded entirely by the Department of Veterans Affairs Office of Research & Development. The goal of MVP is to partner with Veterans receiving their care in the VA Healthcare System to study how genes affect health. To do this, MVP will build one of the world's largest medical databases by safely collecting blood samples and health information from one million Veteran volunteers. Data collected from MVP will be stored anonymously for research on diseases like diabetes and cancer, and military-related illnesses, such as post-traumatic stress disorder.

NIH will also invite Veterans to enroll in the PMI Cohort Program at participating VA medical centers

# VA-NINDS collaboration for clinical trial of DBS in PD

- **May 2002** inter-agency agreement between NIH and VA established to evaluate **deep brain stimulation as a treatment for Parkinson's Disease**.
- **CSP #468: A Comparison of Best Medical Therapy and Deep Brain Stimulation of Subthalamic Nucleus and Globus Pallidus for the Treatment of Parkinson's Disease** was a six-year study designed to compare medical to surgical treatment in PD and to compare the benefit of two strategies for surgical treatment of PD.
  - Conducted at seven VA medical centers and six university hospitals
  - Looked at 299 PD patients aged 37 to 83 and compared symptoms between those who had undergone the surgery and those who had used drug therapy alone.
  - Results indicated patients who underwent DBS had better control of their limbs and could walk better than those using medication.
  - Potential side effects from DBS included a decrease in neurocognitive functioning and increases in the rate of infections, falls, depression, gait and balance problems, and pain—and that these side effects were more likely to occur than side effects from medication.
  - DBS did not help other symptoms of PD, including depression; decline in mental ability; and trouble with gastrointestinal, urinary or sexual functions.



# VA-NINDS collaboration for clinical trial of DBS in PD

## CSP#468F: Follow-up Study for treatment of Parkinson's Disease with Deep Brain Stimulation

- In 2009, the VA and NINDS approved an extension study to determine whether the motor benefits of DBS persist beyond 2 years of follow-up, including:
  - Determination of whether the specific stimulation target (GPi vs STN) affects the durability of long-term motor improvement
  - Defining the impact of DBS on long-term function and quality of life in patients with PD
  - Identifying clinical features that predict favorable or unfavorable long-term outcome
  - Describing the long-term performance of the DBS devices.

**NINDS agreed to contribute an additional \$4.1m for the follow-up study, which ran from 2010-2015.**

# Research on Fatigue

- NIH Portfolio analysis indicates that **\$163 million** was awarded in general fatigue-related research (including chronic fatigue) since FY14.
  - Less than one-third of the funds directed at fatigue explored any type of biological mechanism. Most of the research focuses on fatigue as a symptom of aging or disease.
- Investigators identified the following challenges:
  - Investigators studying fatigue are working in silos (cancer, HIV/AIDS, ME/CFS, etc.)
  - lack of correlation between subjective and objective measures of fatigue
  - Need for taxonomy of fatigue considering the different domains (cognitive, emotional, physical)
  - Significant need for validated measures of fatigue to be used across study populations
  - No consensus in field about role/importance of restorative sleep and the link to fatigue
  - Very little ongoing research on underlying mechanisms of fatigue

# Fatigue Workshops in FY17

*February 3, 2017 and March 15, 2017*

- Facilitate workshops to bring investigators together from all areas of fatigue research
- Goals of February workshop:
  - Define the metrics by which investigators measure and study fatigue (both subjective and objective measures in both humans and animal models)
  - Identify and define what the domains researchers are looking at (cognitive, emotional, physical)
  - Identify the measures/instruments and determine which need to be validated to measure fatigue domains
  - Identify wearables and innovative ways to study fatigue
- Goals of March workshop:
  - Discuss mechanisms by which sleep alleviates fatigue.
  - Determine the role of glymphatics in the mechanisms of fatigue and the impact of sleep.
  - Review animal models utilized to study sleep and circadian rhythms that can be used to study fatigue.
  - Identify knowledge of how energetics and metabolomics impact sleep and fatigue.

# Plans for an Interagency Fatigue Working Group

- Agencies in the **Department of Transportation** plan to initiate an interagency working group that includes HHS agencies:
  - Federal Aviation Administration interested in safety and performance of commercial pilots and are investigating biomarkers of fatigue
  - National Highway Safety Administration (NHSA) interested in measures and biomarkers of fatigue and drowsiness



# 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
- NIH Plans for CFS/Myalgic Encephalitis Research
  - 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

# Research in Chronic Fatigue Syndrome

- Trans-NIH ME/CFS Working Group

- **Goals**

- Advance research on the cause, prevention, diagnosis, pathophysiology and treatment of ME/CFS
    - Communicate ME/CFS research information with ICs, OD

- **Activities**

- Organize Federal Partners meeting (follow-up to 2014 Pathways To Prevention (P2P) Workshop)
      - Develop disease parameter
      - Create new knowledge
        - » Diagnostics, Epi studies, Prognostics
        - » Causation- immunologic, neurologic, genomic
      - Develop outcome measures
      - Develop and test treatment
      - Training and education



# NIH Funding Opportunity Announcement

## Notice of Intent to Publish RFAs released on Friday, October 22, 2016

- Multi-disciplinary, multi-site ME/CFS collaborative research centers and a data management coordinating center
- Foster use of common protocols and common data elements across sites to enable longitudinal studies of large cohorts of individuals with ME/CFS
- Enable and support research at academic centers
- Partner with Clinical Science Translational Awards (CTSAs) where possible to provide infrastructure
- Encourage involvement of young and new investigators (both basic science and clinical)
- Require community engagement and involvement to ensure success
- Discussions underway to partner with international partners to expand network of ME/CFS Collaborative Research Centers

# The BRAIN Initiative®

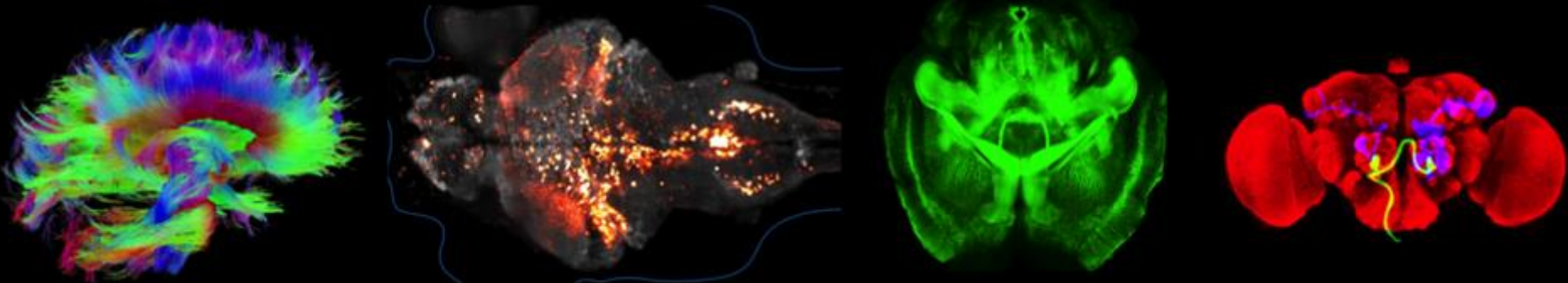
## BRAIN 2025 *A SCIENTIFIC VISION*

Brain Research through Advancing Innovative  
Neurotechnologies (BRAIN) Working Group  
Report to the Advisory Committee to the  
Director, NIH

June 5, 2014



- 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

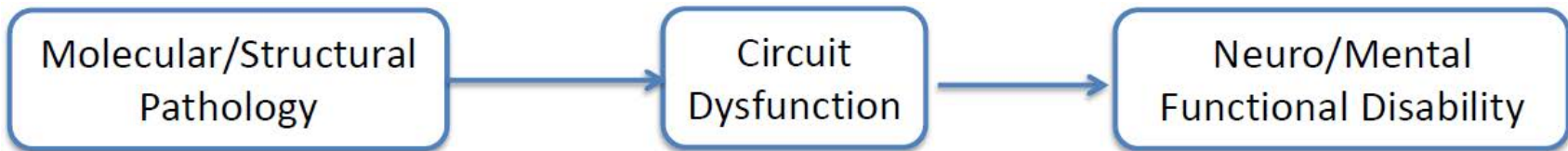




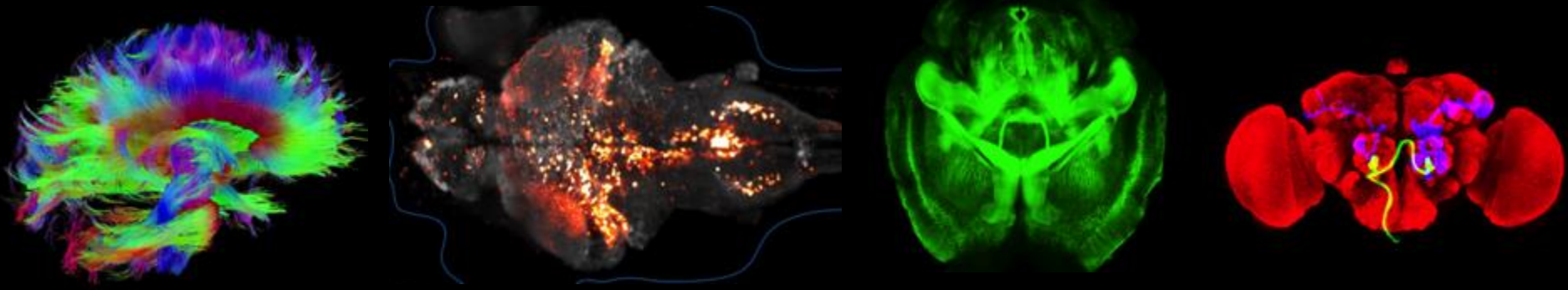
# What's the problem? It's the circuits stupid!

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.

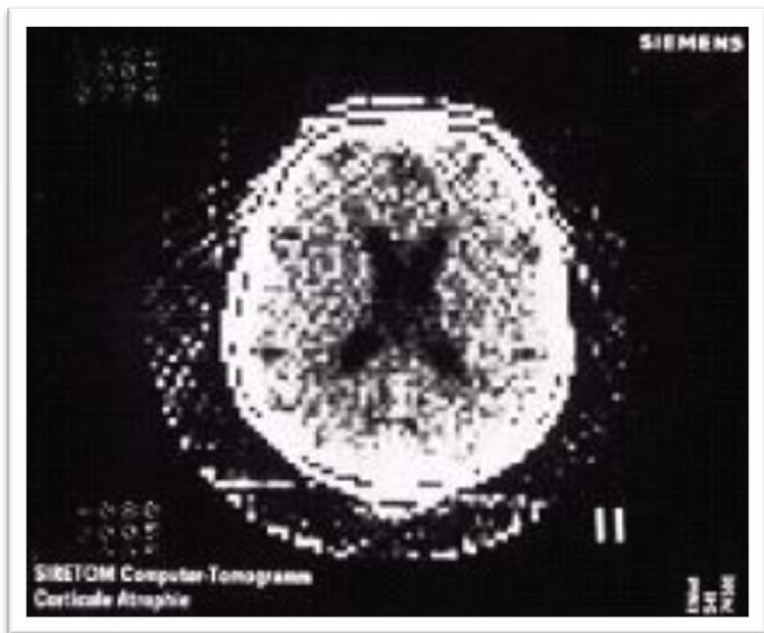


- Goal: Make circuit normalization/compensation the target of intervention: Pharmacologic/Cell/Device/PT,OT, Speech Therapy



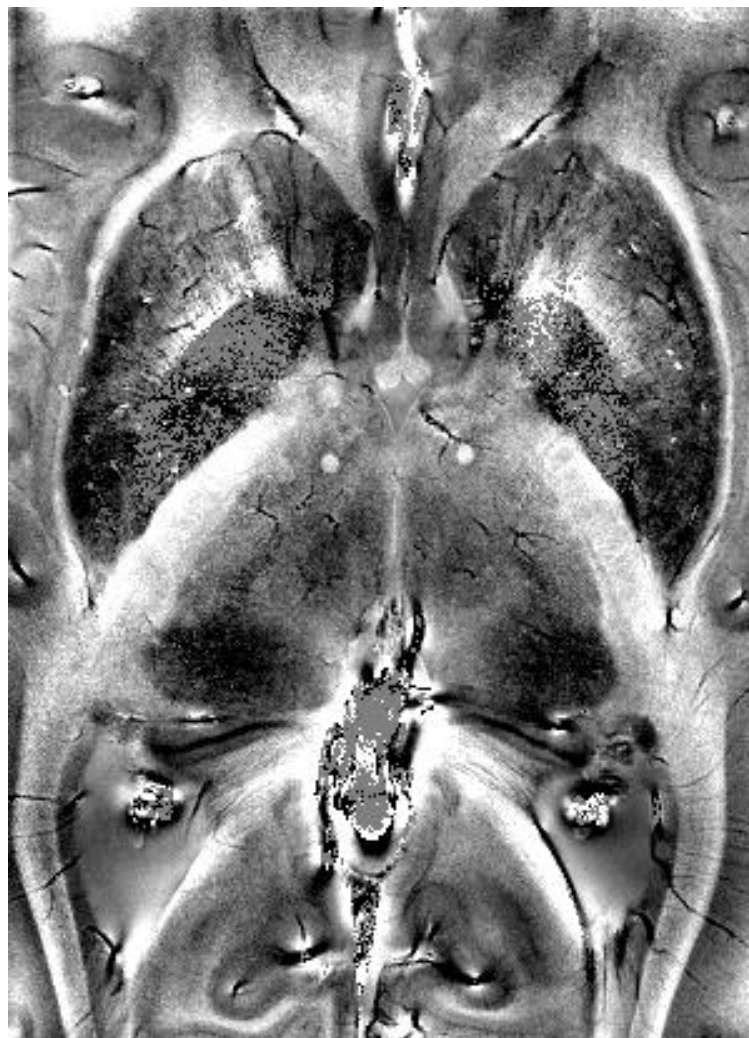
# What Is Next?

1974



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

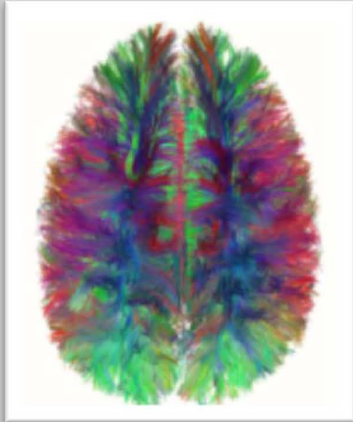
2016



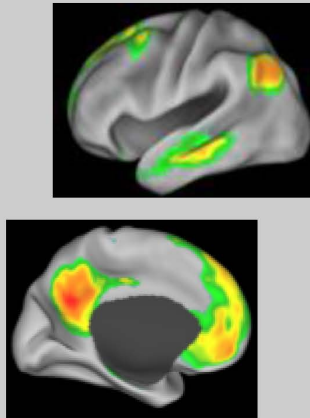
42T susceptibility MRI imaging  
Jeff Duyn, NIH

# NIH Connectome Project Mapping the Human Connectome

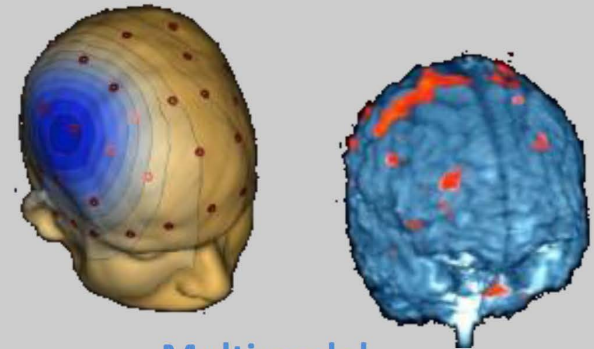
Structural  
Connectivity



Functional  
Connectivity

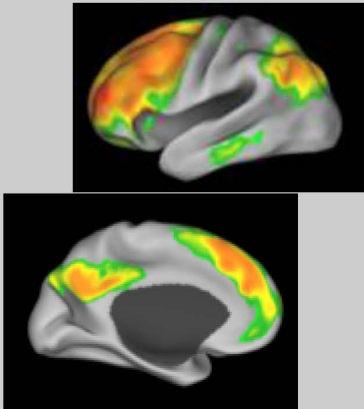


Temporal  
Connectivity

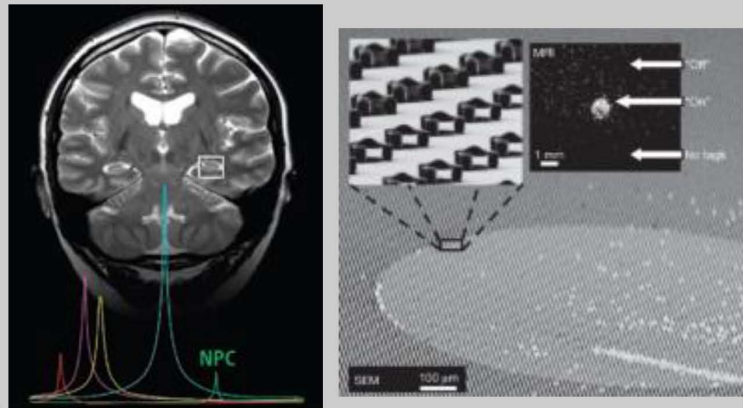


Multimodal  
Integration

Molecular Imaging



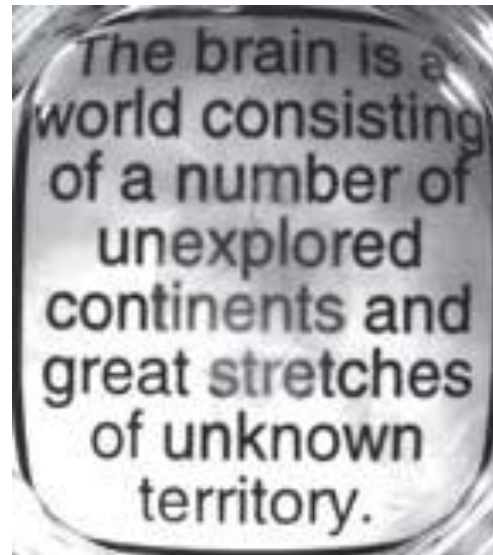
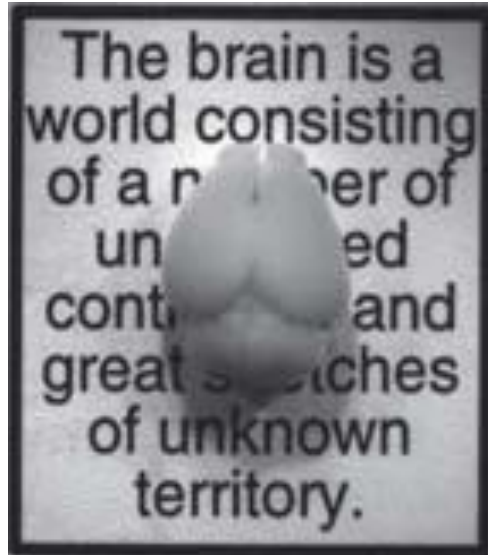
New Molecular Imaging



Wash U  
U Minn  
MGH

# CLARITY: *Neuroanatomy for the 21<sup>st</sup> Century*

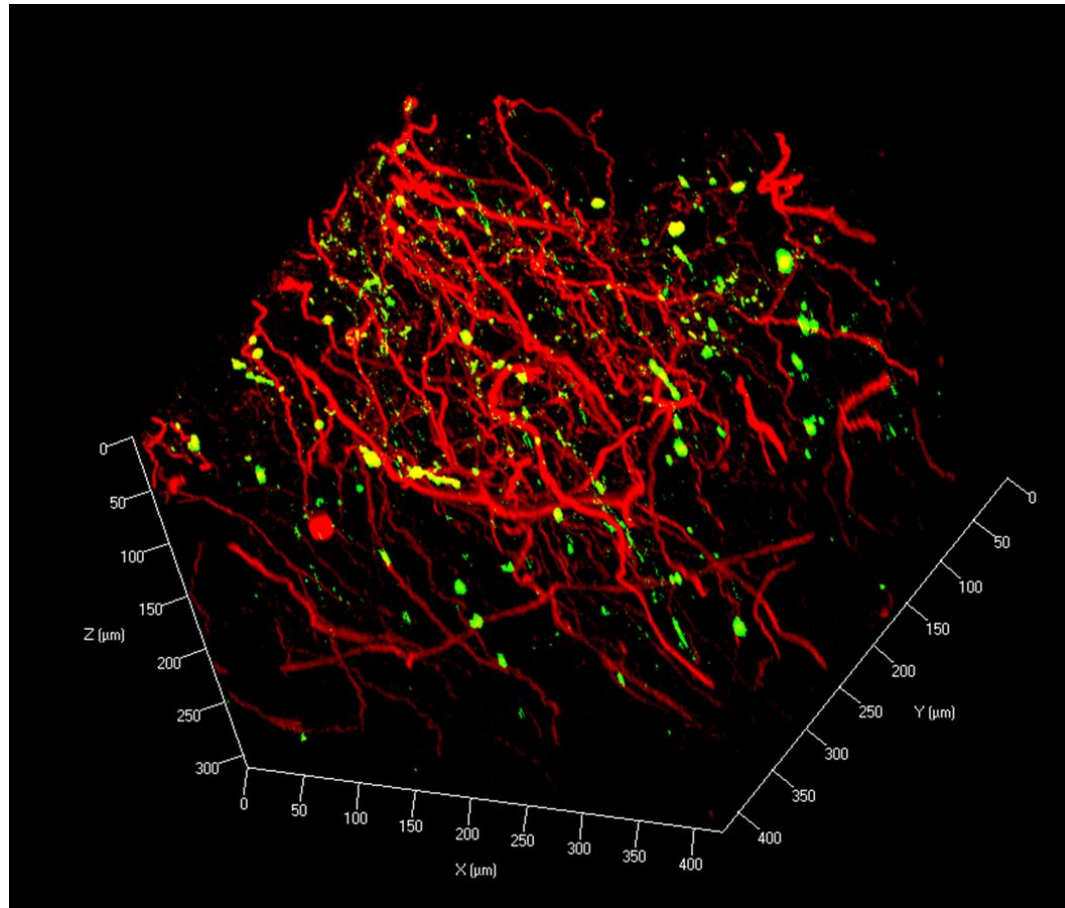
Deisseroth et al, Stanford



# 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- $\alpha$ SN (green) and anti-TH (red) antibodies on human midbrain block (z-stack step size  $1.5 \mu\text{m}$ ).



Neuropathology and Applied Neurobiology

7 DEC 2015 DOI: 10.1111/nan.12293

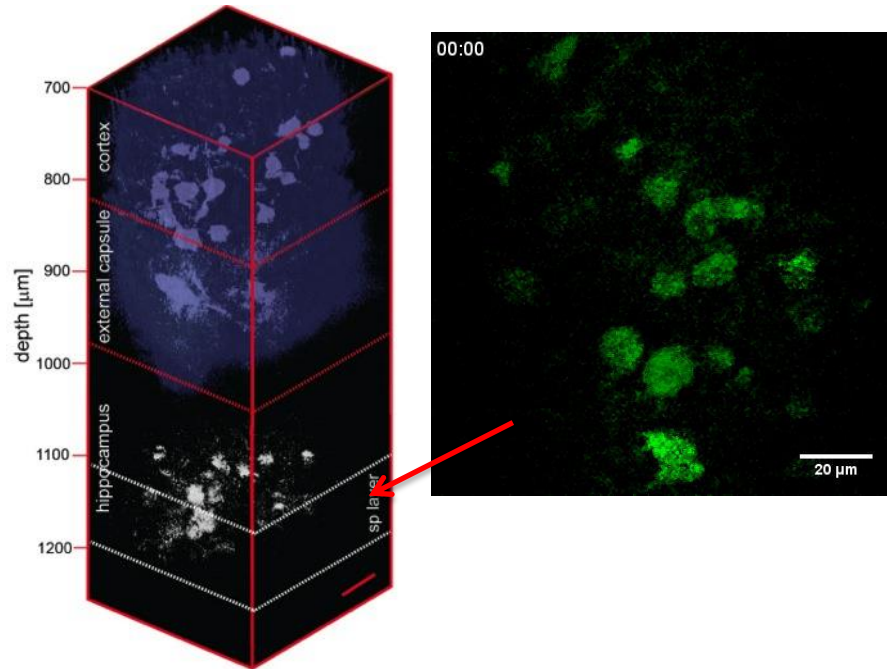
<http://onlinelibrary.wiley.com/doi/10.1111/nan.12293/full#nan12293-fig-0006>

# Optical Instrumentation

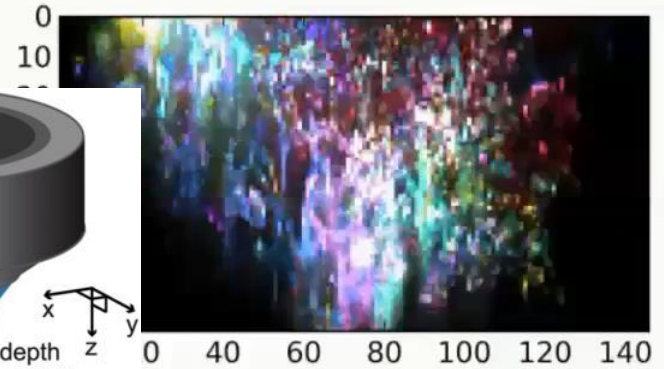
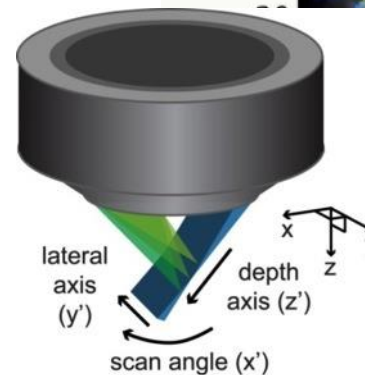
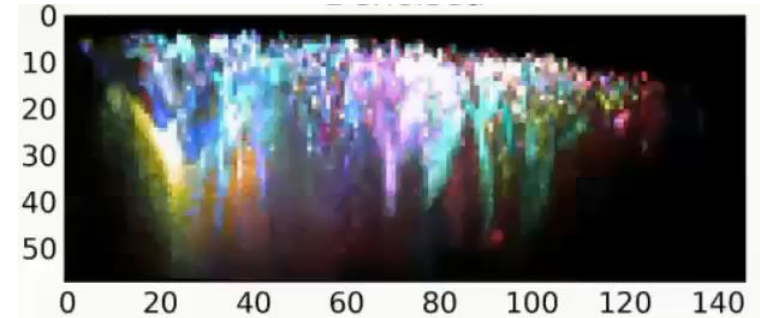
*Deeper – anywhere in the brain*

*Faster – whole volumes rather than single image plane*

*More precise targeting*

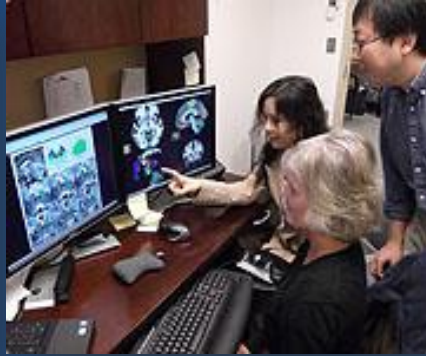


3-photon imaging of hippocampal neurons >1mm deep in the mouse brain – *Cornell (Xu)*



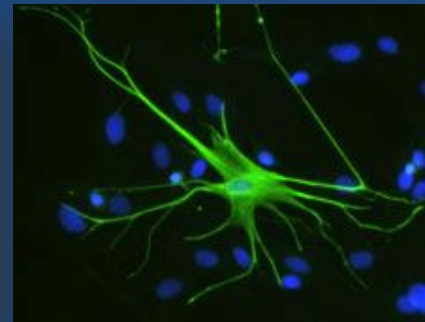
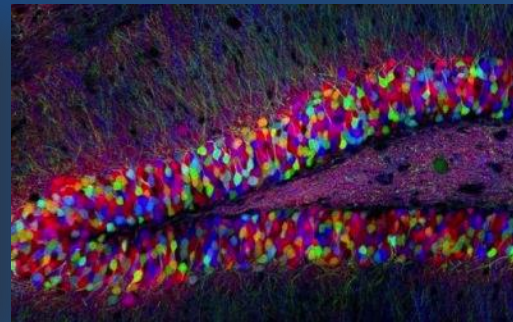
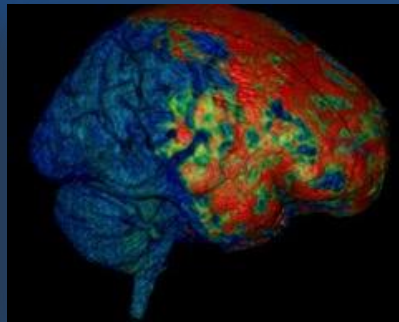
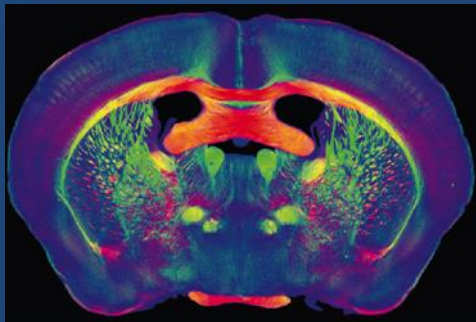
SCAPE imaging of cortical neurons colored by deconvolution – *Columbia (Hillman, Paninski)*





# NINDS

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



# Questions?

**Walter J. Koroshetz, M.D.**

**Director**

**National Institute of Neurological Disorders and Stroke**

**Email: [koroshetzw@ninds.nih.gov](mailto:koroshetzw@ninds.nih.gov)**

**Website: <http://www.ninds.nih.gov/>**



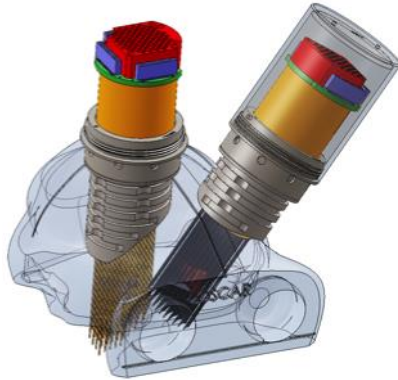
**Follow me [@NINDSdirector](https://twitter.com/NINDSdirector)**



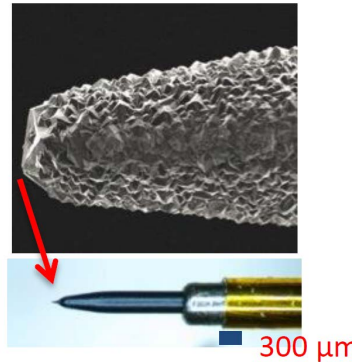
# **Supplemental Slides**

# Electrode Development

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

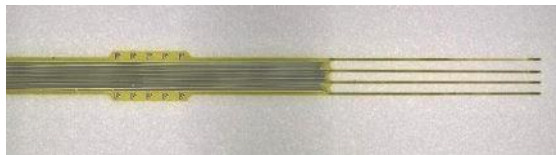
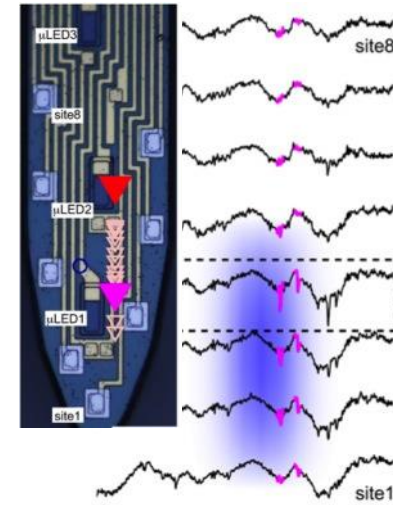


Dual 96 channel electrode microdrives targeting vmPFC and anterior Insula in NHP  
-- Graymatter Research Inc.

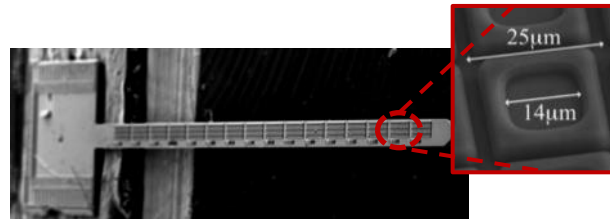


Diamond electrode for stable and calibrated transmitter measurement -- Mayo Clinic

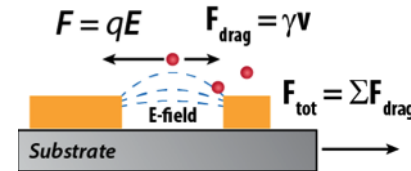
Integrated micro-LEDs for selective optogenetic control  
-- U. Michigan



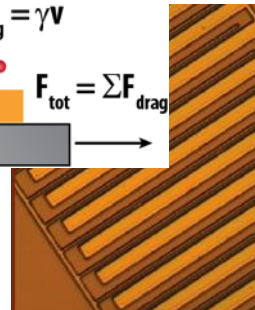
Flexible polymer probe - long-lasting, high-density recordings  
-- Lawrence Livermore National Labs



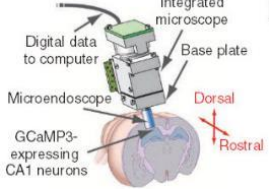
CMOS multi-electrode array with >500 contacts  
-- Italian Institute of Technology



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



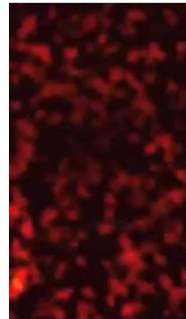
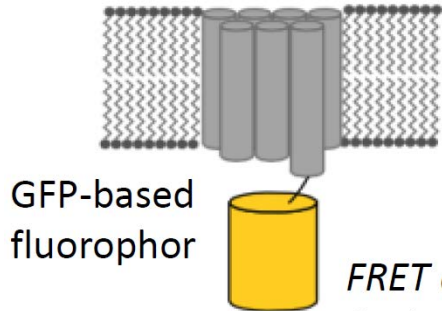
# Probe Development



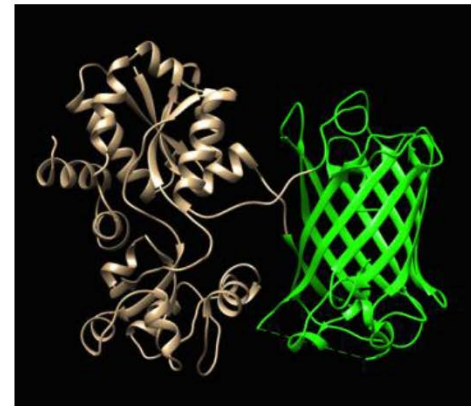
**Sensors: voltage, transmitters/modulators, activity history, activated synapses, MRI for calcium**

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

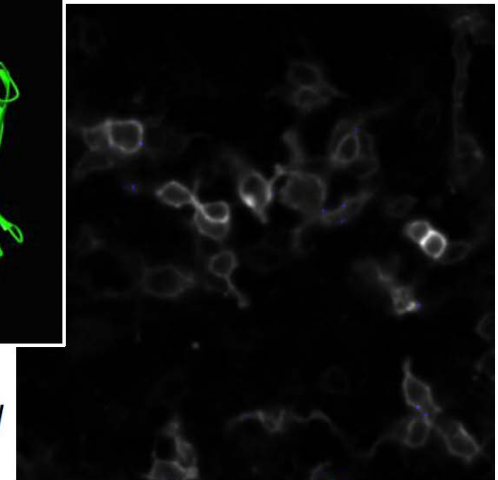
Mutated Opsin *Fast response to voltage changes*



*FRET donor for bright signal*



*GFP Linked bacterial protein mutated to bind serotonin*



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

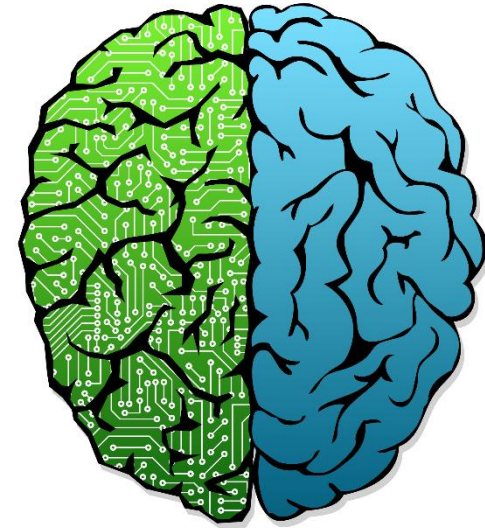
New optogenetic serotonin sensor with high SNR in cultured cells – *UC Davis (Tian)*



# BRAIN Neuroethics

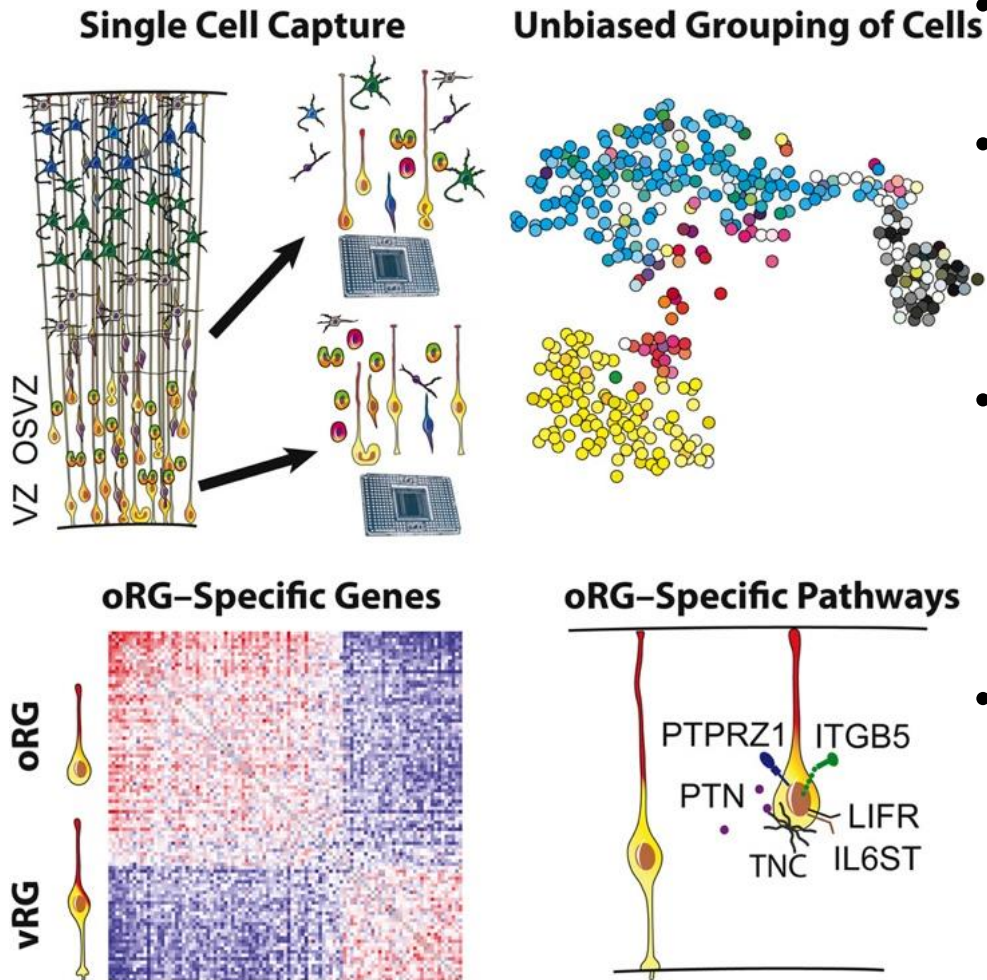
## BRAIN Neuroethics Workgroup

- A consultative ethics group to work with BRAIN leadership and BRAIN investigators
- Co-chaired by Dr. Christine Grady and Hank Greely
- Services:
  - Advise NIH on neuroethics questions important for BRAIN that could be answered through focused empirical research
  - Draft relevant guidance documents to address critical ethical issues associated with BRAIN research
  - Consider proposed funding areas for BRAIN projects for questions of ethical risk
- Workgroup meeting February 9<sup>th</sup> with BRAIN PIs conducting invasive human studies
- New joint BRAIN/Blueprint neuroethics project team (Team N)
- <http://braininitiative.nih.gov/about/newg.htm>



# BRAIN: *Exciting Advances*

## Molecular Diversity of Single Cells from Human Cortical Germinal Zone

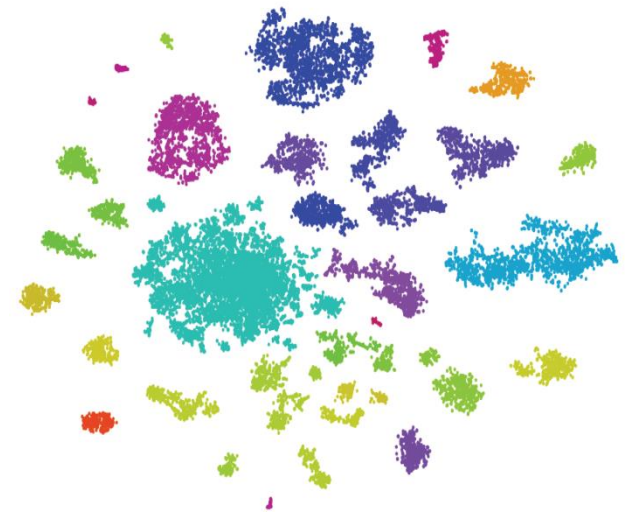
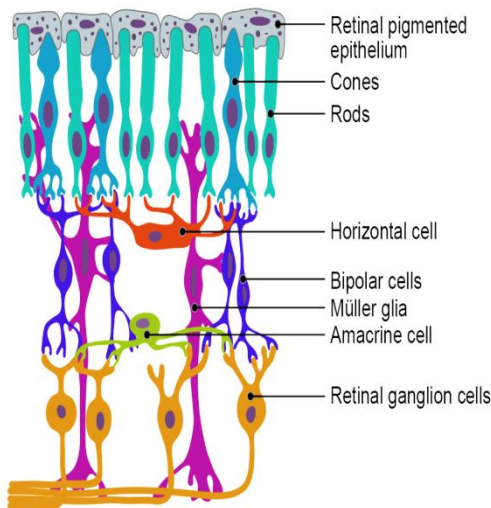
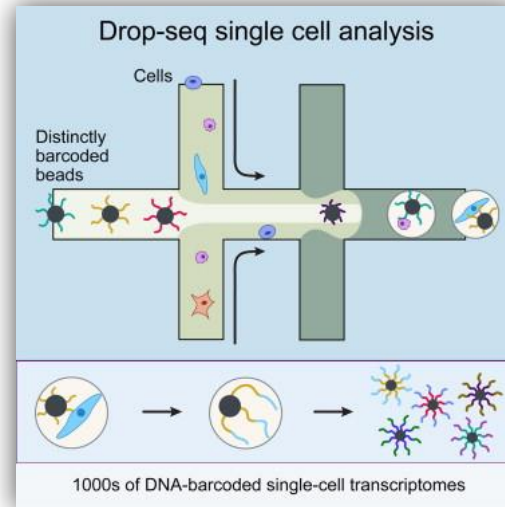


- PI: Kriegstein, AR and colleagues, *Cell*
- Analyzed gene expression in single human radial glia cells
- Demonstrate that the ventricular zone (VZ) and outer subventricular zone (OSVZ) contain molecularly distinct subpopulations of human radial glia
- Single radial glia cells from the OSVZ:
  - generate hundreds of daughter cells of diverse types
  - Maintain stem cell niche
- Suggests potential role in the evolutionary expansion of the human neocortex

# 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



# 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**



# BRAIN Projects for Neurorehabilitation

## High-bandwidth Wireless Interfaces for Continuous Human Intracortical Recording

*Leigh Hochberg, Massachusetts General Hospital*

- Goal: restore **communication and independence** to tetraplegic patients
- Fully implanted neural recording system (100 neurons) sending signals to receivers 1 meter away
  - no cords, reduced infection risk
  - input signals to computer cursor or neuromuscular stimulators
- BrainGate3 Neural Interface System being tested in 6 participants in their homes for a year

## Central Thalamic Stimulation for Traumatic Brain Injury (TBI)

*Nicholas Schiff, Weill Medical College of Cornell University*

- Goal: improve therapy for severe to moderate TBI with **chronic cognitive impairment**
- Obtain and use neuroimaging, computational modeling, behavioral, and electrophysiological data from humans
- Serve as early clinical feasibility study to support development of next generation central thalamic deep brain stimulation devices

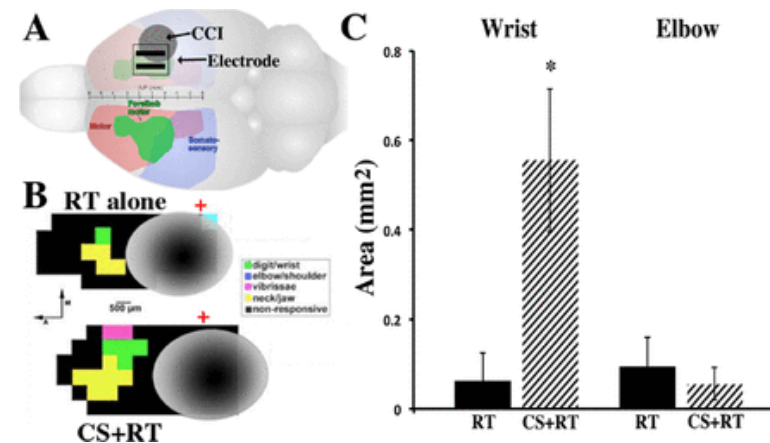


# BRAIN Projects for Neurorehabilitation

## Cortical Stimulation to Enhance Motor Recovery Following Traumatic Brain Injury

Deanna Adkins, Medical University of South Carolina

- Goal: combine cortical stimulation with motor rehabilitative therapy to **improve motor function** following TBI
- Rat model: behavior, quantitative light microscopy, and intracortical microstimulation mapping
- Understand neural basis of effective vs ineffective treatment
  - Optimize stimulation parameters
  - Track changes to cortex structure
  - Determine effective sensitive period
  - Endurance of treatment



# Trans-NIH ME/CFS Working Group

**Walter Koroshetz, M.D., Chair**

National Institute of Neurological Disorders and Stroke

**Vicky Whittlemore, Ph.D., NIH Representative to HHS CFS Advisory Committee**

National Institute of Neurological Disorders and Stroke

**Harvey J. Alter, M.D., MACP**

NIH Clinical Center

**Catherine Bennett, Ph.D.**

(Alternate: Christine Melchior, Ph.D.)

NIH Center for Scientific Review

**Joseph Breen, Ph.D.**

(Alternate: Joshua Milner, M.D.)

National Institute of Allergy and Infectious Diseases

**Milton Corn, M.D.**

National Library of Medicine

**Emmeline Edwards, Ph.D.**

National Center for Complementary and Integrative Health

**Basil Eldadah, M.D., Ph.D.**

National Institute on Aging

**Bill Elwood, Ph.D.**

Office of Behavioral and Social Science Research

**Yolanda Vallejo-Estrada, Ph.D.**

National Institute of Dental and Craniofacial Research

**Adam Felsenfeld, Ph.D.**

National Human Genome Research Institute

**Rohan Hazra, M.D.**

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development

**Mike Humble, Ph.D.**

(Alternate: Jonathan Hollander, Ph.D.)

National Institute of Environmental Health Sciences

**Joyce Hunter, Ph.D.**

National Institute on Minority Health and Health Disparities

**Kathy Jung, Ph.D.**

National Institute on Alcohol Abuse and Alcoholism

**Cheryl Kitt, Ph.D.**

NIH Office of Extramural Research

**Martha Matocha, Ph.D.**

(Alternate: Leorey Saligan, Ph.D., RN, CRNP)

National Institute of Nursing Research

**Cheryl L. McDonald, M.D.**

(Alternate: Shimian Zou, Ph.D.)

National Heart, Lung, and Blood Institute

**Christopher Mullins, Ph.D.**

National Institute of Diabetes and Digestive and Kidney Diseases

**Ann O'Mara, Ph.D., R.N., M.P.H.**

National Cancer Institute

**Matthew Rudorfer, M.D.**

National Institute of Mental Health

**David Thomas, Ph.D.**

National Institute on Drug Abuse

**Todd Wilson, D.O.**

(Alternate: David Eckstein, Ph.D.)

National Center for Advancing Translational Research

**James Witter, M.D., Ph.D.**

National Institute of Arthritis and Musculoskeletal and Skin Diseases

**Steve Zullo, Ph.D.**

National Institute on Biomedical Imaging and Bioengineering

# Active 'Gulf War Illness' Projects

Project Title	Funding Institute	Funding Amount
<a href="#"><u>LIVE IMAGING OF BRAIN CIRCUITRY IN MOUSE MODELS OF PTSD</u></a>	NIMH	\$546,263
<a href="#"><u>NERVOUS SYSTEM DEVELOPMENT AND PLASTICITY</u></a>	NICHD	\$911,968
<a href="#"><u>EXERTIONAL EXHAUSTION IN CFS</u></a>	NINDS	\$340,156
<a href="#"><u>GENDER DIFFERENCES IN MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME</u></a>	NINDS	\$100,00 (supplement)
<a href="#"><u>GENDER DIFFERENCES IN MYALGIC ENCEPHALOMYELITIS/CHRONIC FATIGUE SYNDROME</u></a>	NINDS	\$487,064
<a href="#"><u>LEAD AND OTHER NEUROTOXINS AS RISK FACTORS FOR AMYOTROPHIC LATERAL SCLEROSIS</u></a>	NINDS	\$119,784