

DEPARTMENT OF DEFENSE
BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

3-5 NOVEMBER 2015

NINDS Perspective on the Relationship between Head Trauma and CTE

Patrick SF Bellgowan, Ph.D.
Program Director for TBI,
NINDS / NIH

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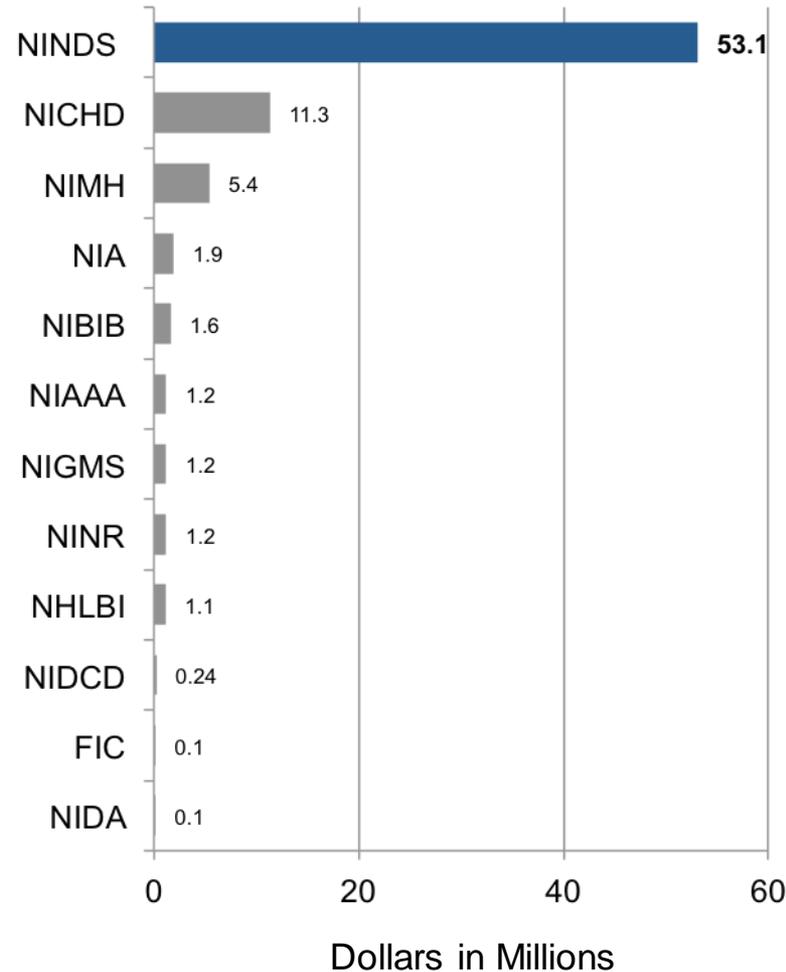


Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

TBI research is supported by many NIH Institutes



FOGARTY





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Center for Neuroscience and Regenerative Medicine

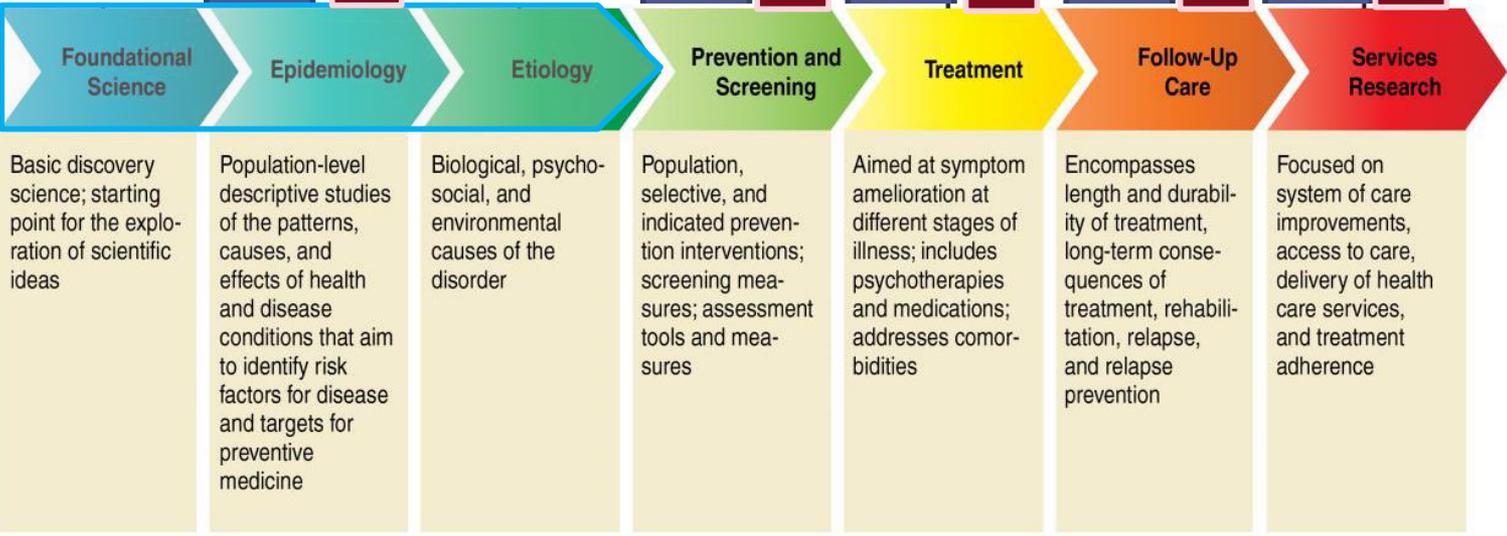
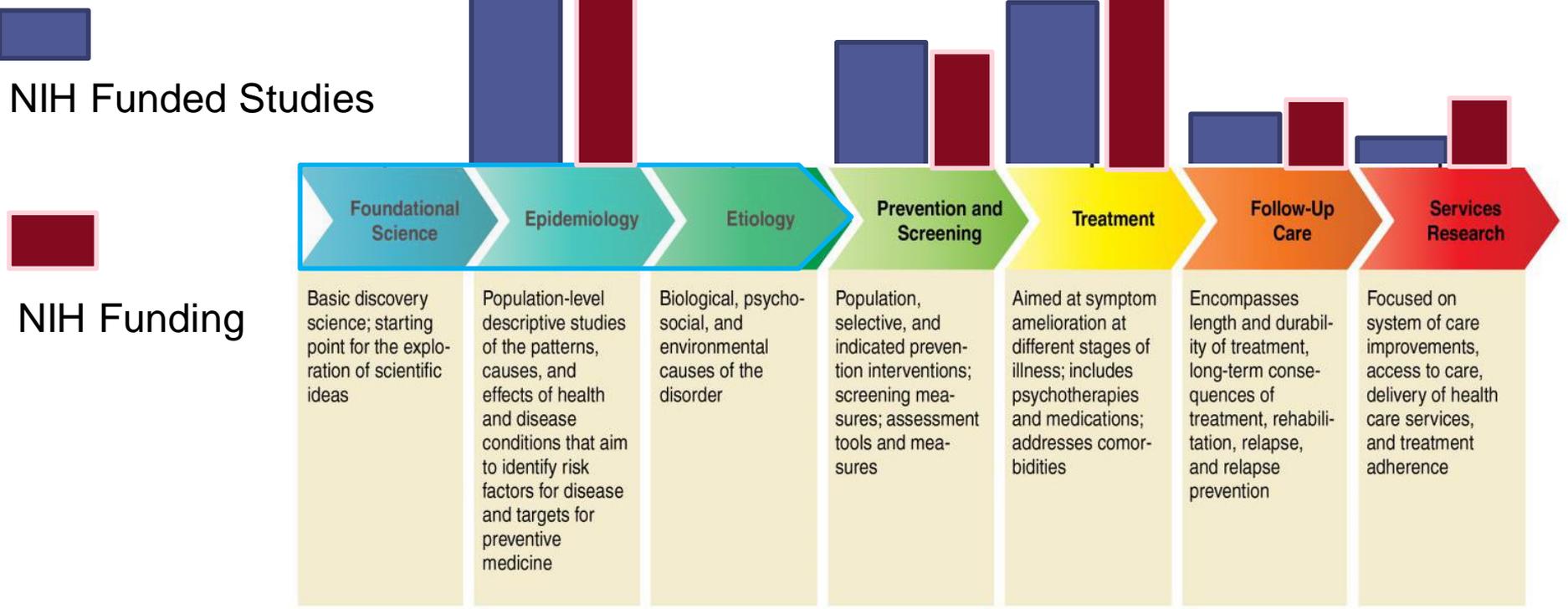


A collaborative effort, involving Intramural NIH/Uniformed Services University/WRNMC to advance the knowledge and treatment of TBI with a special focus on forms of TBI relevant to military

- Diagnostics & Imaging
- Biomarkers
- Neuroprotection & Modeling
- Neuroregeneration
- Neuroplasticity
- Rehabilitation & Evaluation



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

- In FY15, NINDS funds ~\$3.25M in CTE research of which the NFL donation accounts for \$3.00M.



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Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Wednesday, September 5, 2012

The National Football League Commits \$30 Million Donation to the Foundation for the National Institutes of Health to Support Medical Research



The Foundation for the National Institutes of Health (FNIH) announces that the National Football League (NFL) has agreed to donate \$30 million in support of research on serious medical conditions prominent in athletes and relevant to the general population.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Questions for CTE Research

The workshop stimulated a great deal of discussion and a number of key research questions to inform the research community and the Federal agencies in advancing our understanding of CTE, its risk factors, how to diagnose it and how to better prevent and treat the disorder.

- ▶ What are the population prevalence and incidence of CTE?
- ▶ What are the number of impacts to the head and their magnitude that cause CTE?
- ▶ Is participation in contact sports a CTE risk factor for school-aged children and young adults?
- ▶ Is exposure to single or multiple blast exposures a risk factor for CTE in returning service members?
- ▶ Are there genetic susceptibilities to CTE?
- ▶ How can CTE be diagnosed in living people?
- ▶ Can PET studies using novel tau ligands detect CTE in living persons?
- ▶ Are CTE and single exposure TBI distinct pathologic processes or part of a disease spectrum?
- ▶ What neuropathology protocols should be followed to define minimal sampling requirements for CTE in a large autopsy-based study?
- ▶ What retrospective and prospective screening protocols should be followed to facilitate identification of potential CTE cases in brain banks?
- ▶ What are the relevant animal models of CTE pathology, especially TBI-related tau abnormalities?



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Sports and Health Research Program

In the study Collaborative Research on Chronic Traumatic Encephalopathy and Delayed Effects of Traumatic Brain Injury: Neuropathology and Neuroimaging Correlation, teams headed by researchers at Mount Sinai Hospital and Boston University are working jointly to:

- More fully characterize the neuropathology associated with chronic traumatic encephalopathy (CTE) and delayed effects of traumatic brain injury through systematic, rigorous, and collaborative studies of post-mortem biospecimens;
- Validate the neuropathological criteria for a post-mortem diagnosis of CTE and delayed post-traumatic neurodegenerative diseases through independent and blinded analyses;
- Understand the incidence and prevalence of CTE;
- Identify neuroimaging signatures of the neuropathology as a foundation for the development of new diagnostic tools.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

NINDS Strategy for CTE funding

Neuropathology of CTE

Post-mortem



Antemortem



Former Pro and College Ath



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NINDS Strategy for CTE funding



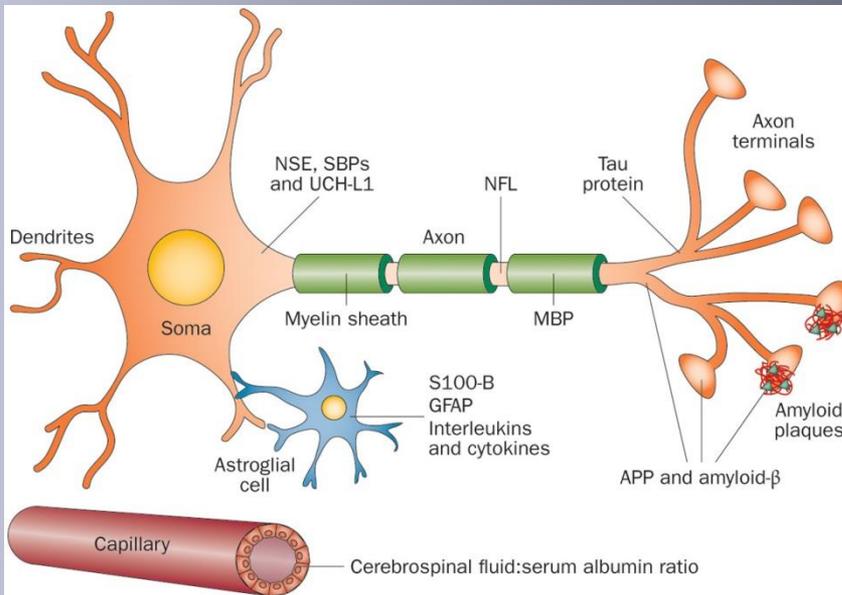
GAP



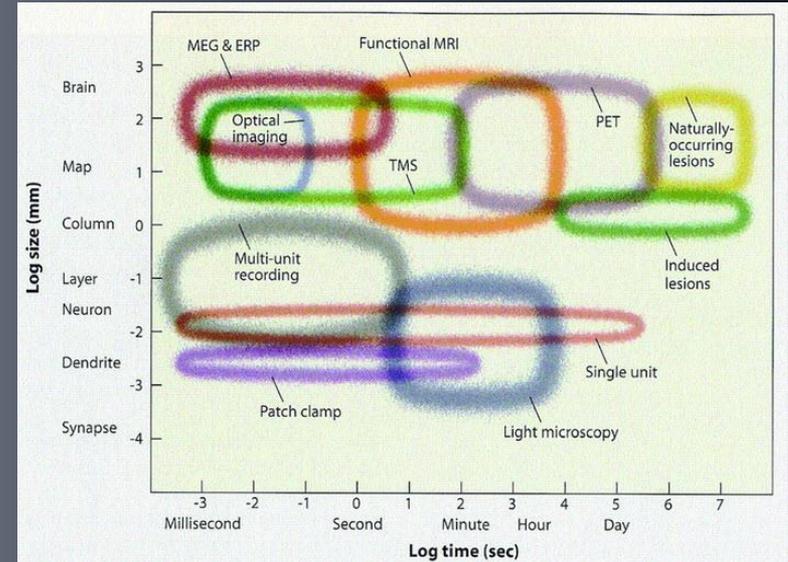


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NINDS Strategy for CTE funding



Zetterberg, H. et al. (2013)
Nat. Rev. Neurol.





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Funding Opportunity Title	Collaborative Research on Chronic Traumatic Encephalopathy and Delayed Effects of Traumatic Brain Injury: Neuropathology and Neuroimaging Correlation (U01)
Activity Code	U01 Research Project – Cooperative Agreements
Announcement Type	New
Related Notices	<ul style="list-style-type: none">• August 21, 2013: Removed reference to ASSIST in section IV.3, since ASSIST is currently only available for multi-project applications.• May 1, 2013 - See Notice NOT-AG-13-009. Notice of NIA's Participation.• March 29, 2013 - See Notice NOT-DC-13-004. Notice of Participation of NIDCD.• March 21, 2013 - See Notice NOT-DA-13-015. Notice of NIDA's Participation.• March 21, 2013 - See Notice NOT-NS-13-019. Notice of Change in Eligibility of Foreign Institutions.
Funding Opportunity Announcement (FOA) Number	RFA-NS-13-013

The initiative will support a multicenter, systematic and comprehensive investigation of the neuropathology of Chronic Traumatic Encephalopathy and the delayed effects of traumatic brain injury using postmortem biospecimens, and histological and neuroimaging tools as a foundation for future studies to develop in vivo diagnostics.



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Neuropathology of CTE and Delayed Effects of TBI: Toward In-Vivo Diagnostics

PI : **Gordon, Wayne**

Mount Sinai School of Medicine

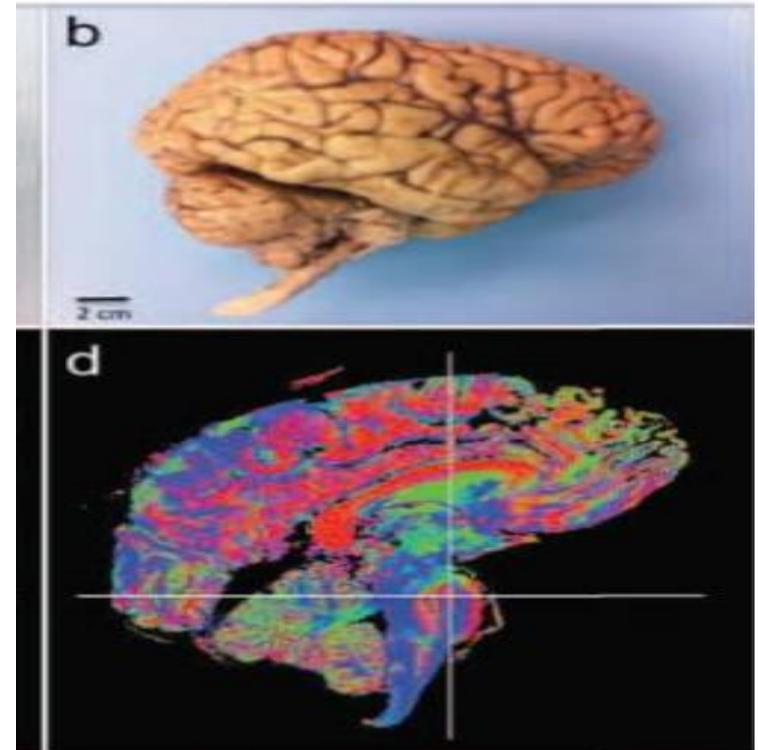
Dates: 09/01/2013 – 08/30/2017

Gap: Is CTE a distinct condition and if so what are its defining neurocognitive and neuropathological characteristics.

Goals: A more complete understanding of the long-term neuropathological sequelae of single TBI. Leverage access to the Adult Changes in Thought study.

Deliverables

- 1) Characterize the neuropathology.
- 2) Identify neuroimaging signatures.
- 3) Estimate the incidence and prevalence.





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

CTE and Posttraumatic Neurodegeneration: Neuropathology and Ex Vivo Imaging

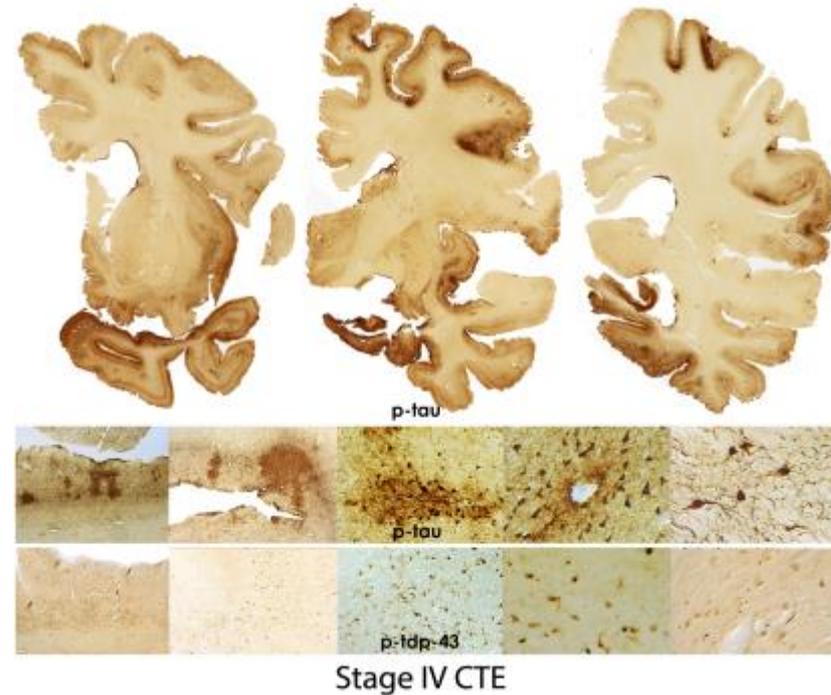
PI : McKee, Ann

Boston University

Dates: 09/01/2013 – 08/30/2017

Gap: Is CTE a distinct condition and if so what are its defining neuropathological characteristics.

Goal: To evaluate the late effects of TBI, including single and repetitive TBI of varying severity, and CTE, using histological examination of postmortem biospecimens and neuroimaging tools as a foundation to develop in vivo diagnostics.



- Goals:
- ~100 postmortem brains from high risk subjects
- ~250 new brains anticipated
- **Consensus conference to validate dx of CTE using a team of neuropathologists**
- MRI and PET of postmortem brains



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?



NEUROSCIENCE

Researchers seek definition of head-trauma disorder

Guidelines should assist in diagnosis of brain disease seen in retired American footballers.

Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy

Nigel J. Cairns - Washington University, St. Louis

Dennis W. Dickson - Mayo Clinic, Jacksonville

Rebecca Folkerth – Brigham and Women’s Hospital, Boston

C. Dirk Keene - University of Washington, Seattle

Ann McKee - Boston University (Principal Investigator of one of the NIH CTE grants)

Daniel Perl - Uniformed Services University of the Health Sciences, Bethesda

Thor Stein - Boston University

Willie Stewart - University of Glasgow, Scotland

Jean Paul Vonsattel - Columbia University, New York



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy

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:

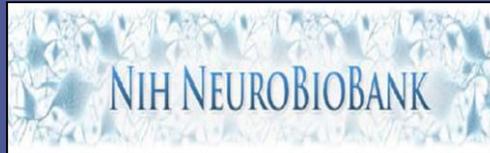
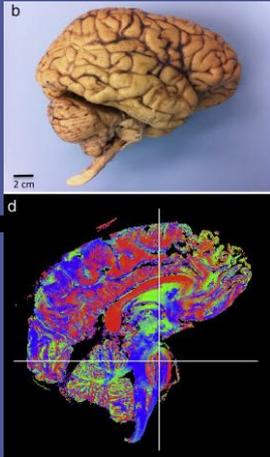
1. Macroscopic abnormalities in the septum pellucidum (cavum, fenestration), disproportionate dilatation of the IIIrd ventricle or signs of previous brain injury;
2. Abnormal tau immunoreactive neuronal lesions affecting the neocortex predominantly in superficial layers 2 and 3 as opposed to layers 3 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.



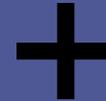
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Neuropathology of CTE

Post-mortem



Prevalence





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

A banner for the NIH NeuroBioBank featuring a background of blue and white neuron-like structures. The text "NIH NEUROBIOBANK" is centered in a blue serif font.

NIH NEUROBIOBANK



Center for Neuroscience and Regenerative Medicine
Brain Tissue Repository

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



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NINDS Neuroscience Funding Announcements

Detect, Define and Measure the Progression of Chronic Traumatic Encephalopathy (U01)

Funding Contact: [NINDS Funding Coordinator](#)

Funding Categories: [Repair and Plasticity](#)

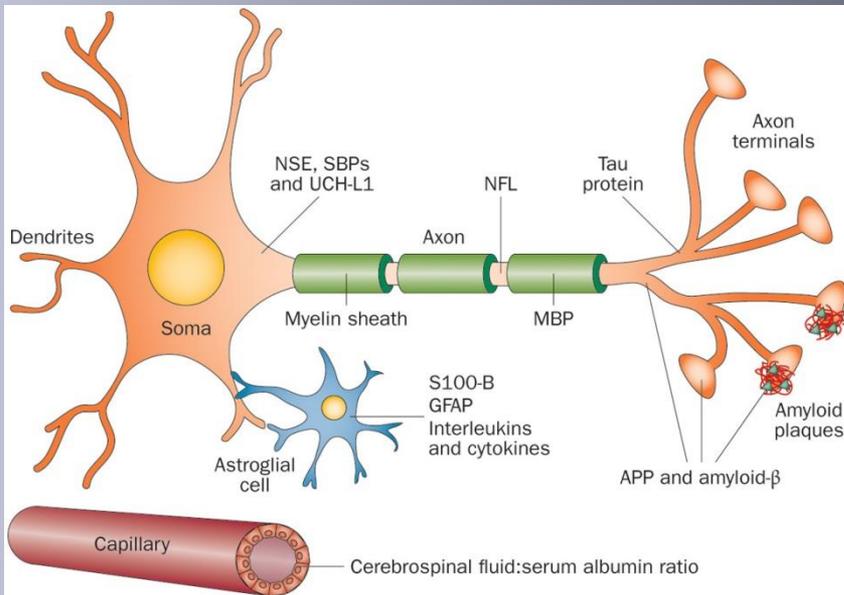
Brief Description:

The purpose of this initiative is to detect, characterize and measure the progression of neurodegeneration in individuals with a probable or possible diagnosis of chronic traumatic encephalopathy (CTE) using brain imaging and other biomarkers. The overall goals are increased knowledge concerning the neurological mechanisms and ways to detect CTE as it evolves over a 3 - 5 year period and the development of a consensus diagnosis to inform clinical trials aimed at preventing or slowing disease progression in the future.

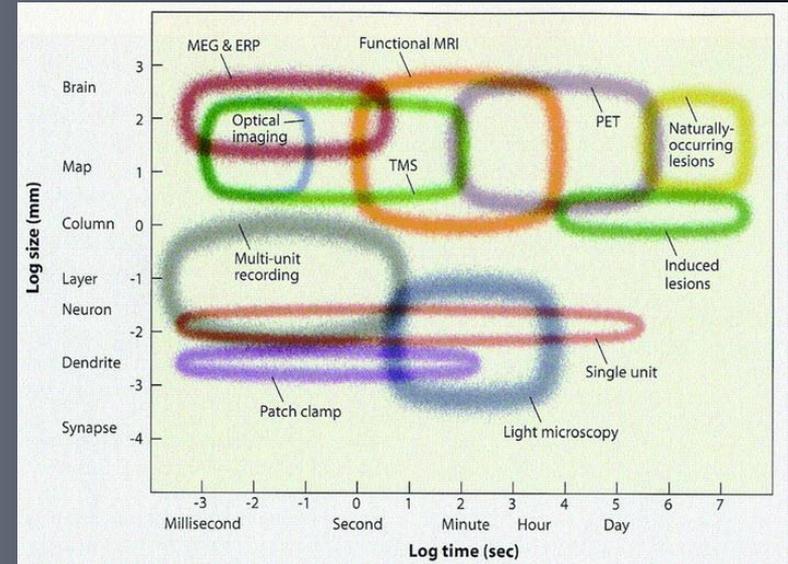


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Zetterberg, H. et al. (2013)
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(~\$2.3M / year for 7 years)



PET imaging,
Biofluids

Behavioral testing,
QOL

MR Imaging,
Symptom





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Comparing Studies: NINDS Common Data Elements

- First set developed in 2010
 - Well-suited for hospital-based studies of acute TBI in adults
- 2012: Second version of TBI CDEs, organized around 4 major study types
 - Epidemiological research
 - Studies on acute, hospitalized patients
 - Studies of the rehabilitation for moderate/severe TBI
 - Mild TBI/Concussion research

NINDS Common Data Elements
Harmonizing Information. Streamlining research.

Standards Tools Learn

Streamline Your Neuroscience Clinical Research using these content standards that enable clinical investigators to systematically collect, analyze, and share data across the research community.

The NINDS strongly encourages researchers who receive funding from the Institute to ensure their data collection is compatible with the common data elements (CDEs).

CDEs now available:

- [General \(CDEs that cross diseases\)](#)
- [Epilepsy](#) New!
- [Spinal Cord Injury](#)
- [Traumatic Brain Injury](#)

CDEs in development:

- [Stroke](#) - Public comments under review
- [Parkinson's Disease](#) - Final development
- Frontotemporal Dementia
- Huntington's Disease
- Amyotrophic Lateral Sclerosis
- Neuromuscular Disease
 - Congenital Muscular Dystrophy
 - Friedreich's Ataxia
- Headache

[Investigators and Research Teams - launch studies with CDEs](#): The CDE Standards

[Data Managers and Programmers - incorporate the CDEs into your systems](#): Use

[Discover how the CDE Project collaborates with others](#): Learn more about the

- NINDS formed the International TBI Steering Committee to direct the update & further development of TBI CDEs
- The pre-clinical CDEs are available in the FITBIR data dictionary, NINDS website and the manuscript describing their development is under Review at Neurotrauma. (http://www.ninds.nih.gov/research/tbi/pre-clinical_cde_table%20-%20PDF.pdf)



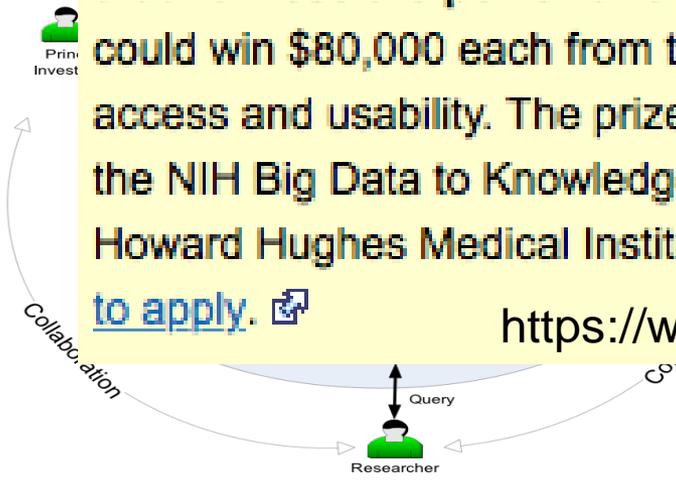
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Interagency Collaborations

Open Science Prize: a new global competition to develop products or services that harness the power of big data to improve health. Six international teams could win \$80,000 each from the Prize to develop prototypes that improve big data access and usability. The prize has been launched through an agreement between the NIH Big Data to Knowledge Initiative and Wellcome Trust, with support from Howard Hughes Medical Institute. Applications due February 29, 2016. [Learn how to apply.](https://www.openscienceprize.org)

<https://www.openscienceprize.org>

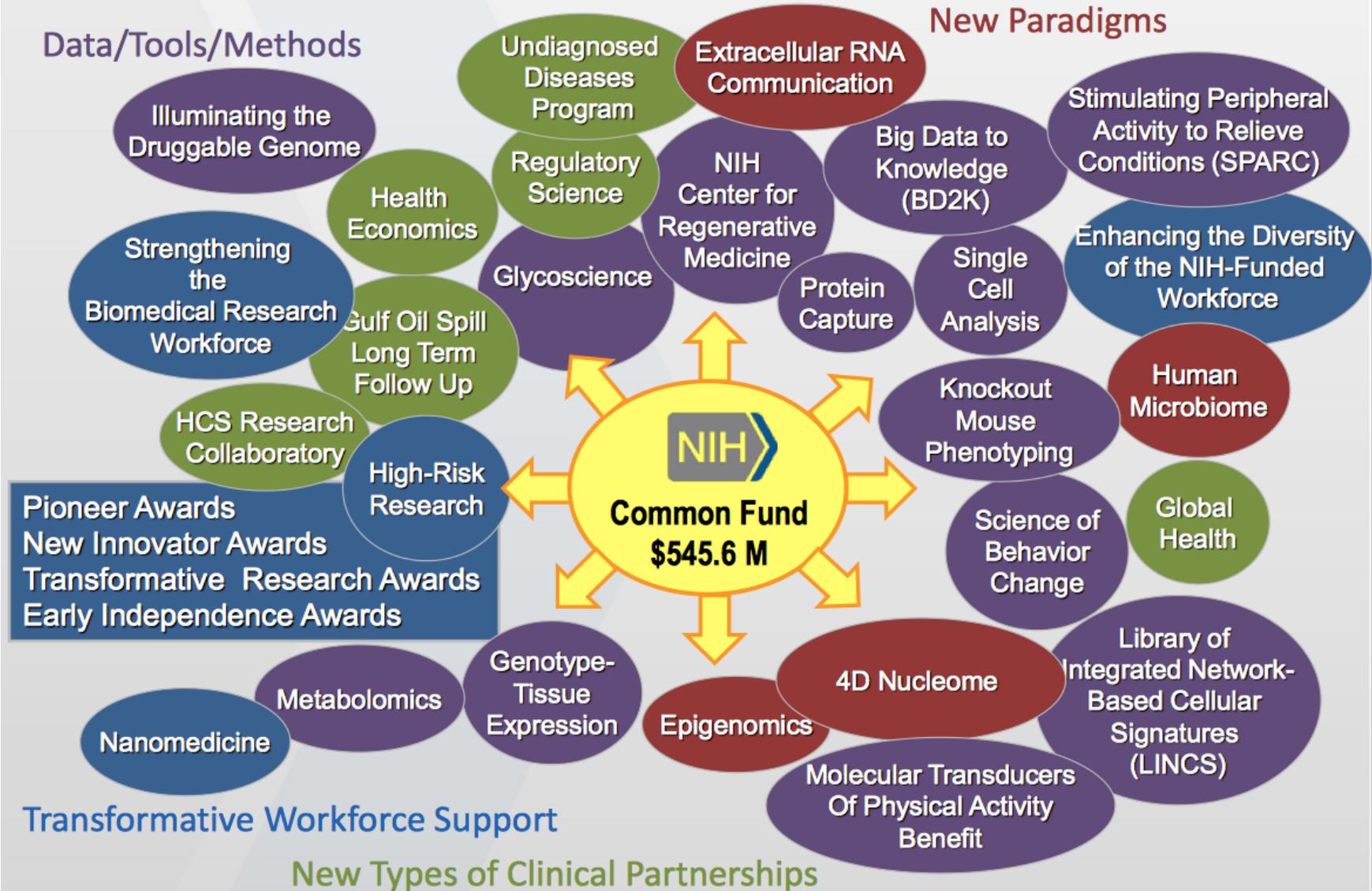


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Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Current Common Fund Programs (FY15)





Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?



National Institutes of Health
Office of Strategic Coordination - The Common Fund

WE ACCELERATE DISCOVERY



Current Funding Opportunities

Title	NIH Guide	RFA Number	Common Fund Contact	Application Receipt Date
Collaborative Activities to Promote Metabolomics Research (Admin Supp)	10/9/15	PA-16-005	Keren Witkin witkinkeren@mail.nih.gov 240-276-6230	2/15/2016
Metabolomics Data Analysis (R03)	10/30/15	RFA-RM-15-021	Barbara Spalholz spalholb@mail.nih.gov 240 276-6230 Art Castle castlea@mail.nih.gov 301 594-7719	Letter of Intent: 1/11/2016 Receipt Date: 2/11/2016



Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

Train in Big Data as the Data is being collected.

NIH Data Science at NIH

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Data Science Community

BD2K

Commons

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BD2K initiative issues new software development FOA.

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ENHANCING NEURO IMAGING GENETICS THROUGH META ANALYSIS

Disease Working Groups

Bipolar

Major Depression

Schizophrenia

ADHD

Epilepsy

HIV

PTSD

Addiction

Parkinson's

Stroke Recovery

OCD

22q11.2

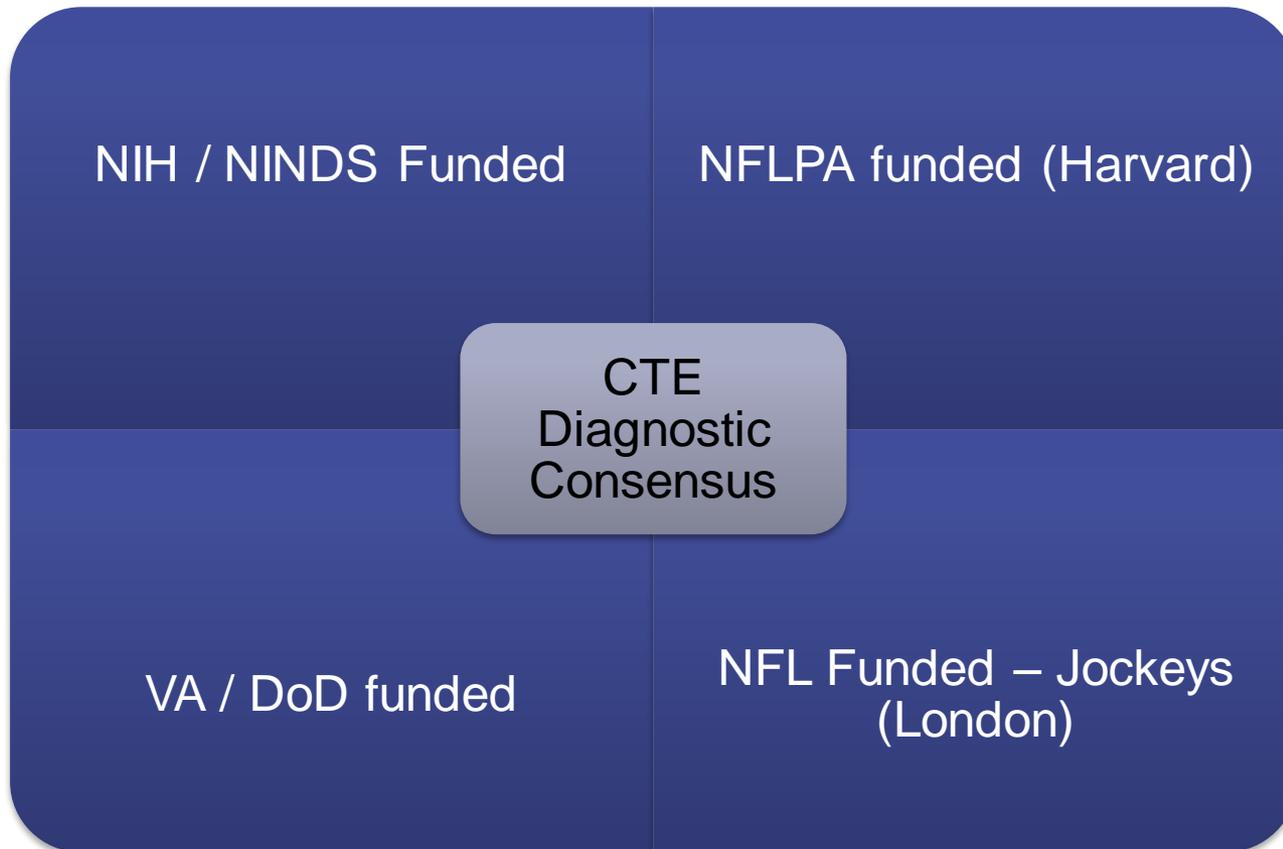
Autism

Anorexia



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Responsibility of the Funding Partners: Insure communication among efforts

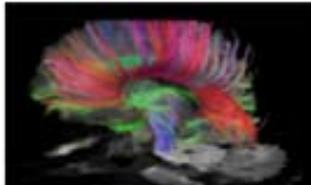




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<http://www.ninds.nih.gov/research/tbi/index.htm>

Traumatic Brain Injury Research (TBI)



Neuroimaging is one of many tools used to investigate TBI.

NINDS supports research on traumatic brain injury (TBI) to advance knowledge on mechanisms of injury and recovery, and to develop better diagnostic tools and more effective treatments. This website provides information on NINDS activities, opportunities and

resources for TBI research.

To receive regular updates on funding announcements and other opportunities, please join the [NINDS TBI Research Listserv](#).

[NIH RePORTER](#), an online reporting tool, allows users to search a repository of NIH-funded TBI research projects and access publications and patents resulting from NIH funding. Please visit [NINDS TBI](#) for more general information.

Listen to TBI investigators discuss data sharing through the FITBIR Informatics System to accelerate TBI research progress on [NIHNINDS YouTube](#).

New! [Researchers seek definition of chronic traumatic encephalopathy \(pdf, 504 kb\)](#)

New! [Pre-Clinical Common Data Elements Table \(pdf, 39 kb\)](#) and [Worksheet \(pdf, 323 kb\)](#) are now available.

Program Contact for TBI Research

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[Joanna Vivalda, R.N., M.B.A.](#)
Clinical Trial Specialist
Clinical Research
joanna.vivalda@nih.gov



Dr. Walter Koroshetz, Director of NINDS

Dr. Walter Koroshetz, Director of NINDS, discusses TBI and the research progress in TBI through data sharing.