Chronic Effects of Neurotrauma Consortium (CENC) 2013–2019

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Chronic Effects of Neurotrauma Consortium





Combat Concussions



- 16-20% of OEF-OIF-OND Veterans who received VA medical care have confirmed TBI and 8% were still symptomatic when initiating care at VA
 - ~200,000 total (>1,100,000 screened) in VA
 - 90,000 symptomatic
 - >98% mild
 - <2% moderate-severe
 - >50% due to MVC



- 75% of Veterans with symptomatic mild TBI also have at least one mental health diagnosis, most commonly Post Traumatic Stress Disorder (PTSD)
- > 90% will have either PTSD or chronic pain disorder

Concern about long-term effects of injury and persistent symptomatology



CENC 1.0



- CENC is a \$62.2 million, multicenter, VA/DoD research collaboration funded in 2013, linking basic, translational, and clinical neuroscience researchers from the VA, military, academia, and the private sector to effectively address the diagnostic and therapeutic ramifications of mTBI and its long-term effects.
- The overarching goal is understanding the lifetime impacts of military service, combat-associated concussions and being a Veteran, in particular with respect to the development of mental health disorders, Alzheimer's dementia and related neurodegeneration.
- Research linkages between 15 major VA Centers, 12 DoD Military Treatment Facilities/Research Sites, and more than 30 academic research centers in 20 States and the D.C.



CENC Sites

- Barrows Neurological Institute, Phoenix, AZ
- Baylor College of Medicine, Houston, TX
- Boston University, Boston, MA
- Brigham Young University, Provo, UT
- Duke University School of Medicine, Durham, NC
- Eisenhower Army Medical Center, Fort Gordon, GA
- Fort Belvoir Community Hospital, Alexandria, VA
- Fort Eustis, Fort Eustis, VA
- Fort Jackson, Columbia, SC
- Fort Lee, Fort Lee, VA
- Fort Stewart, Fort Stewart, GA
- Hunter Holmes McGuire VA, Richmond, VA
- James A. Haley Veterans Hospital, Tampa, FL
- Iowa City VA Health Care Center
- MacDill Air Force Base, MacDill AFB, FL
- Medical College of Wisconsin, Milwaukee, WI
- Medical University of South Carolina, Charleston, South Carolina
- Michael E. DeBakey VA Medical Center, Houston, TX
- Milwaukee VA Medical Center, Milwaukee, WI
- Minneapolis VA Health Care System
- Mountain Home VA Medical Center, Mountain Home, TN
- Northern California Institute of Research and Education, San Francisco, CA
- Roskamp Institute, Sarasota, FL
- RTI International, Durham, NC
- San Antonio Military Medical Center, San Antonio, TX
- San Francisco VA Medical Center, San Francisco, CA
- South Texas Veterans Healthcare Center, San Antonio, TX
- Uniformed Services University of the Health Sciences, Bethesda, MD
- University of Missouri St. Louis, MO



- University of Washington, Seattle, WA
- University of St. Louis, St. Louis, MO
- University of Hawaii, Manoa, HI
- University of Utah, Salt Lake City, UT
- University of Washington, Seattle, WA
- VA Boston Healthcare System
- VA Portland Health Care System
- VA San Diego Health Care System, San Diego, CA
- Virginia Commonwealth University, Richmond, VA
- WG Hefner VA Medical Center, Salisbury, NC

 Coordinating Center/ Research Site
 Research Core
 Research Site/ Core
 Research Site
 Research Site

CENC Studies

- Longitudinal Study of 82% individuals with combat-concussion (+ other lifetime concussion) and 18% no-concussion who are comprehensively studied (history, symptoms and screens (PCS, depression, PTSD, pain, dementia), exam, MRI, electrophysiology, saliva and serum initially, phone f/u annually and in-person re-evaluation every 5 years for life (n=1,647).
- Retrospective database of 2 million Veterans with clinical care, healthcare utilization, and medications established
- 6 additional prospective, clinical studies completed (n= 600 participants)



 Basic science study of human-tau producing mouse exposed to repetitive concussions and aged.

Development of a concussion-specific DTI phantom to standardize imaging platforms.

Summaries of Protocols and Results

- CENC Special Issue: Brain Injury 2016; 30(12): 1397–1514
 - Methodologies for 10 studies
 - Assessment Protocols and Tools <u>https://www.tandfonline.com/toc/ibij20/30/12?nav=tocList</u>
- CENC Special Issue Brain Injury 2018, 32:9, 1149– 1294
 - Findings for 10 studies through Spring 2018
 - Integration of findings across 7 clinical studies <u>https://www.tandfonline.com/toc/ibij20/32/10?nav=tocList</u>



Figure 1. CENC Accomplishments and the Foundation/Experience for Serving as the Infrastructure for LIMBIC

CENC Infrastructure: At-the-Ready Forces to Deploy Research and Facilitate Knowledge Translation					
Administrative Coordinating Center has successfully ensured the overall establishment, maturation and functioning of all CENC personnel, researchers, studies and Cores				Multi-site, Multi-discliplinary Research Team	Uniform, Standardized Research Approaches across DoD, VA, and Academic Sites
Biomarker	Neuroimaging	Biostatistics, Data and Study Management	Neuropathology- Brain Bank	Geographic Diversity 21 States	"Gold Standards" in Concussion
•~ 1,500 unique blood	• Central reading of	• 7 prospective human	IRB-compliant	• 30 Academic Universities	Uniform, standardized research approaches to
and saliva samples to- date • Plasma, exosomal tau and p-tau associated with repetitive mTBI • GWAS and exosome work underway on CENC and DVBIC 15- Year Study samples (biomarker partners funded through NIH)	 > 2,000 MRIs Ongoing specialty research analyses (volumetric, diffusion, perfusion, functional connectivity) of more than 1,400 MRIs Patented mTBI-specific, DTI Phantom for standardization 	studies, including the 8- center Longitudinal Study's highly standardized, human research protocol • Knowledge translation of data from 10 studies into >50 scientific publications, 100 abstracts and 150 presentations	protocol for dedicated brain bank (interdigitated with VA PTSD Brain Bank) for accepting brain donations from CENC human studies • 12 brain donations to-date and 86 commitments	 15 Veterans Affairs Medical Centers 12 Military Treatment Facilities 75 multi-disciplinary neuroscience researchers to conduct a wide range of basic, translational, clinical, epidemiologic and biomedical sciences research Established links with researchers performing clinical trials to provide a pipeline for referral of participants 	 facilitate replication and validation of findings yielding "gold standards" for the field of concussion: Common Data Elements (CDE) Manualized methods of procedure (MOP) Best Practice approaches for all protocols CENC Longitudinal Study has been deployed with > 1,500 unique research subjects, is published, has been available on the CENC website since inception, and offers a multi- modal evaluation and monitoring model to address the complexity of brain functioning

CENC Findings

• Of the 2,200+ participants recruited:

- more than two-thirds who still had persistent difficulties after combat concussions and related issues are high functioning, employed and managing well in the community more than 7 years after injury.
- the remaining one-third of the cohort with post-concussion symptoms are demonstrating ongoing and increasing difficulties that are requiring significant health care utilization.
- None of the subjects is exhibiting signs of dementia 5-20 (mean = 9) years after most recent injury
- Female subjects have greater symptoms than male.
- Servicemembers and Veterans with combat-related concussions and associated conditions (PTSD, pain, depression, substance use, elevated suicide risk) represent a unique and high-risk population.

CENC Clinical Findings

- Retinal thickness does not correlate well with symptom burden, secondary conditions, vision or time post-injury.
- NeuroImaging (DTI, *f*MRI, McDESPOT, PRISM, MR Volumetrics, Fractional Anisotropy) do not correlate with symptom burden, secondary conditions, or activity
- Central otolith deficits are most disabling, but clinical approaches to diagnoses are limited.
- Computerized eye tracking can be used to differentiate normal from PTSD/mTBI and PTSD from TBI diagnoses.
- Serum biomarkers can differentiate those with 0-1 mTBI vs those with 3+ mTBI

CENC Epidemiology Data

DoD and VA maintain large Veterans' health datasets

In an innovative and cost efficient way, we pooled DoD and VA datasets to determine the effects of TBI (by injury severity) in Service Members and Veterans



60% Increased Risk of Dementia with TBI



Barnes...Yaffe, Neurology, 2014.

Comorbidities Have an Additive Effect on Dementia Risk



Barnes...Yaffe, Neurology, 2014.

Risk of Parkinson's Disease Increases with TBI Severity



Gardner et al, Neurology 2018

Chronic Pain and Pain Disability



<u>Study population</u>: 116,913 Iraq/Afghanistan Veterans who received care from 2007-2015 and completed Comprehensive TBI Evaluation (CTBIE)

Seal et al., Arch Phys Med and Rehab, 2017.

Chronic Opioid Therapy Higher in mTBI + Depression/PTSD



Study population:

53,124 Iraq/Afghanistan Veterans who completed CTBIE and had chronic pain and no opioid prescriptions in prior year

Seal et al., J Pain, 2018.

Risk of Suicide Increases with TBI Severity





Byers et al: under review

CENC Next Steps

- Longitudinal Observational Study (current n = 1,647) is expanding to 11 recruitment sites with annual re-assessment and monitoring for recovery and/or neurodegeneration patterns. Expansion of Biomarker and Imaging assessments.
- Epidemiologic Study (2 million unique subjects) will continue to explore associations between mTBI/co-morbidities and persistence of symptoms (pain, opioid usage, behavioral), recovery patterns, health care utilization, and neurodegeneration.
- Interventional trials will be implemented using the Longitudinal Cohort as appropriate management strategies and approaches are identified.

\$50 million renewal proposal (LIMBIC) submitted January 2019.



75% of chronic diseases and one-third of dementias preventable

Diet, Exercise, Sleep, Stress Management, Pain Care, Productivity, Social Integration, Family, Faith-Based Community













