

# VETERANS HEALTH ADMINISTRATION

## Informational Briefing

### Precision Mental Health and Brain Injury Care: Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC)

Presentation for: Four-Corners Briefing

Presented by: David Cifu, Senior TBI Specialist

Date of briefing: August 18, 2021

# Bottom Line Up Front

- The VA Office of Research and Development (ORD) has several activities in the area of precision mental health and brain health. Today, we will focus on:
  - Long-term Impact of Military-relevant Brain Injury Consortium – Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC)
- LIMBIC-CENC is a nationwide VA/DoD collaboration linking premier translational, and clinical neuroscience researchers from the DoD, VA, academic universities, and private research institutes to address the short and long-term diagnostic and therapeutic impact of combat-related exposures, including mild traumatic brain injury (mTBI) and mental health co-morbidities.
  - Ongoing Longitudinal Study of service members and veterans with combat exposures with and without polytrauma (traumatic brain injury, mental health disorders, pain) has 1,776 participants currently enrolled and assessed, including biomarkers, EEG, MRI, psychometric testing.
  - Ongoing Big Data Study of 2.5 million unique individuals, using a single dataset compiled from VA and DoD electronic health, benefits, pharmacy, and administrative records databases.
  - Prospective data are entered in the Federal Interagency TBI Registry (FITBIR).
- LIMBIC-CENC team engaged in 20+ collaborative research analyses using both LIMBIC-CENC data and data from multiple other TBI studies via FITBIR.

# David Cifu, MD

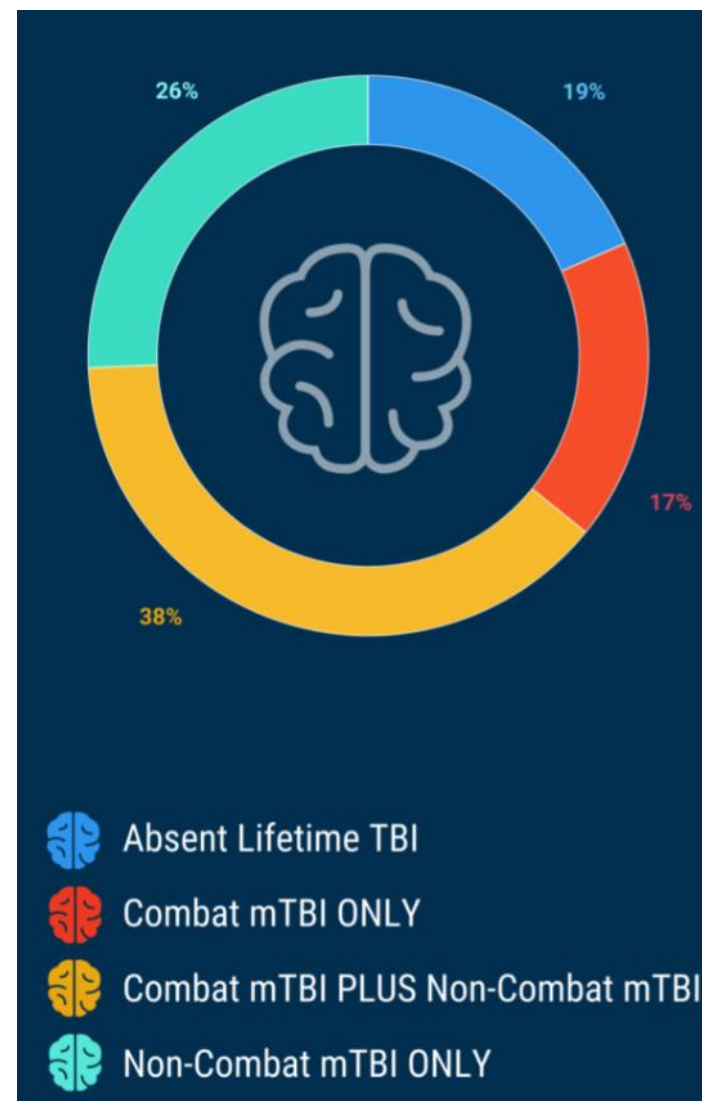
## Senior TBI Specialist for VA

- Physical Medicine and Rehabilitation (PM&R) physician who has cared and advocated for tens of thousands of individuals with acute and chronic disability since 1990.
- Associate Dean for Innovation and Research Neuroscientist in the Virginia Commonwealth University School of Medicine since 1991.
- Physician and researcher at the Richmond VAMC since 2002, who served as the VA National Director for PM&R during the Iraq and Afghanistan Wars, led the Polytrauma System of Care, and works closely with DoD colleagues.
- VA's Champion and Lead Author for the VA/DoD Clinical Practice Guidelines for Persistent Symptoms after mild TBI/Concussion in 2009, 2016 and 2021.
- Author of 225 scientific publications and 40 textbooks.
- Principal Investigator of LIMBIC-CENC since inception in 2013.



# LIMBIC-CENC

- Initiated in December 2013 as part of the National Research Action Plan, which was created under an Executive Order, to address traumatic brain injury (TBI), post-traumatic stress disorder (PTSD) and other mental health conditions to improve diagnosis, treatment and prevention.
- To date, enrolled and characterized 1,776 active participants, with recruitment ongoing (goal = 3,000+ participants)
- Dr. Stuart Hoffman, VA lead for brain health, has been the ORD lead for LIMBIC-CENC since its inception.
- 200+ publications and 500+ presentations through Knowledge Translation Core.





# LIMBIC CENC



Long-Term Impact of Military-Relevant  
Brain Injury Consortium

## Research Cores

### Coordinating Center

- ★ Virginia Commonwealth University, Richmond, VA

### Neuroimaging Core

- ◆ VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

### Biomarkers Core

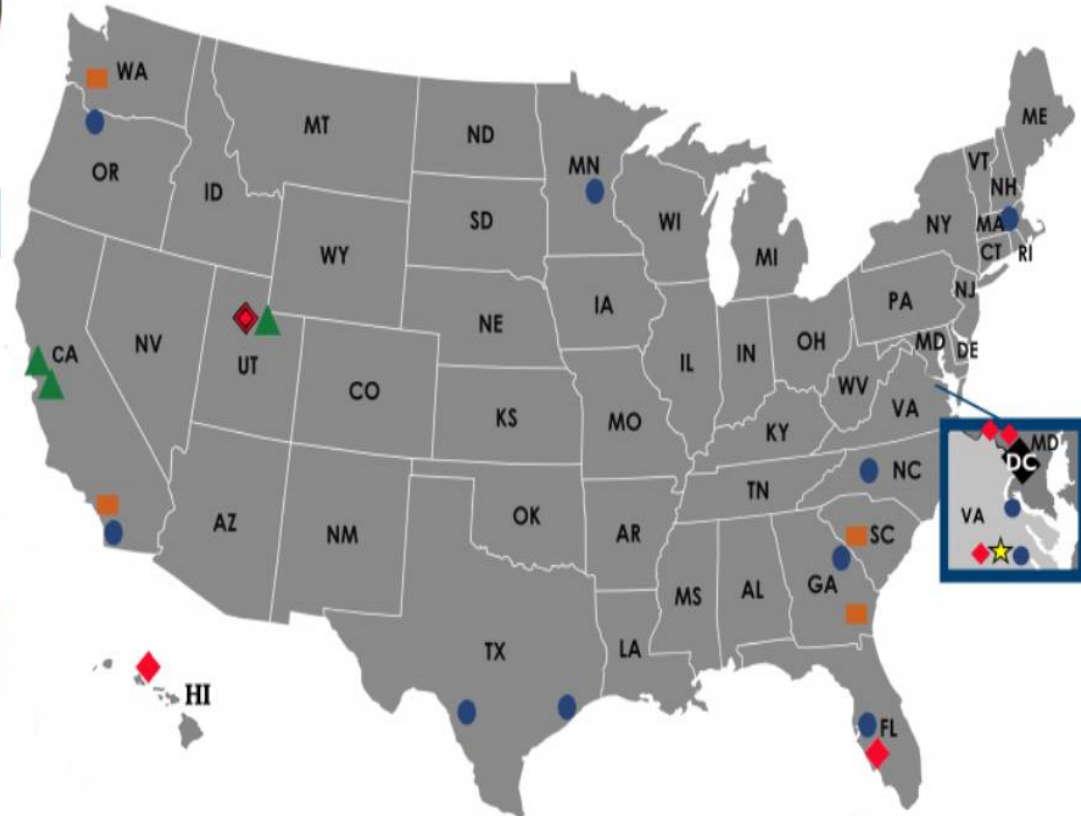
- ◆ Uniformed Services University of the Health Sciences/National Institutes of Health, Bethesda, MD
- ◆ University of Florida Gainesville VAMC, Gainesville, FL

### Data and Biostatistics Core

- ◆ Hunter Holmes McGuire VA, Richmond, VA
- ◆ Virginia Commonwealth University, Richmond, VA
- ◆ VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT
- ◆ University of Hawaii, Department of Speech, Honolulu, HI

## Prospective Longitudinal Enrollment/Recruiting Sites

- Hunter Holmes McGuire VA, Richmond, VA
- Michael E. DeBakey VA Medical Center, Houston, TX
- James A. Haley Veterans Hospital, Tampa, FL
- South Texas Veterans Healthcare Center, San Antonio, TX
- Fort Belvoir Community Hospital, Alexandria, VA
- VA Portland Health Care System, Portland, OR
- Minneapolis VA Health Care System, Minneapolis, MN
- VA Boston Healthcare System, Boston, MA
- WG Hefner VA Medical Center, Salisbury, NC
- VA San Diego Health System/University of California-San Diego/Camp Pendleton, San Diego, CA
- Eisenhower Army Medical Center, Fort Gordon, GA
- MacDill Air Force Base, FL
- Joint Base Lewis-McChord, WA
- Fort Stewart, GA
- Fort Jackson, Columbia, SC
- Naval Amphibious Base, Coronado, CA



## Retrospective Study Sites

- ▲ San Francisco VA Medical Center/University of California-San Francisco
- ▲ VA Palo Alto Health Care Systems/Stanford University
- ▲ University of Utah/VA Salt Lake City Health Care System

★ Coordinating Center

◆ Research Core

▲ Retrospective Study Site

● Prospective Longitudinal Study Site

■ Prospective Longitudinal Recruitment Site



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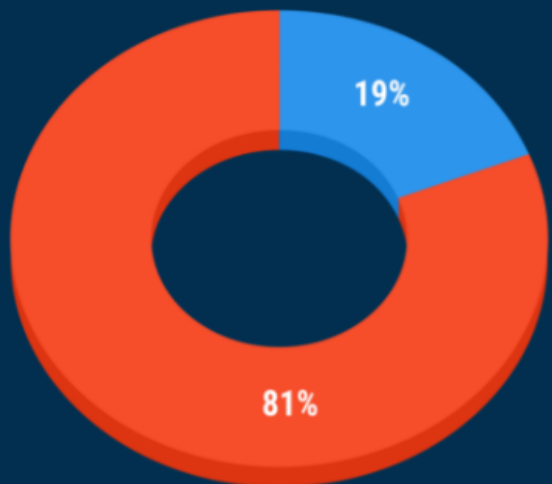
# LIMBIC-CENC Unique Keys to Success

- Nationwide effort that bridges VA and DoD research personnel across combat exposures, blast injury, brain trauma and mental health.
- Leading researchers from across VA, DoD and universities who communicate often, collaborate closely and are highly productive.
- Centralized research infrastructure (study coordination, imaging, biomarkers, statistics, knowledge translation) that can be leveraged across a range of studies.
- Inclusion of consumers (service members, veterans, family members) on both the research team and on the consumer advisory board.
- Knowledge Translation Core dedicated to creating consumer-friendly materials from the research findings.



# LIMBIC-CENC INCLUDES VETERANS WITH A RANGE OF MENTAL AND BRAIN HEALTH DIAGNOSES

## Post-Traumatic Stress Disorder (PTSD)

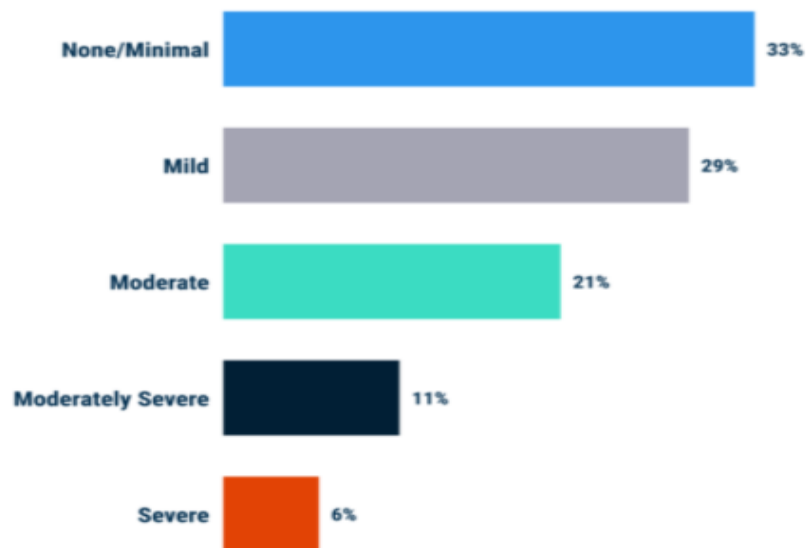


- Probable PTSD (PCL-5 > 48)
- Below cut-off point (PCL-5 < 48)

\* Based on the scores from PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (PCL-5)



## Depression Symptoms



- None/Minimal (0-4)
- Mild (5-9)
- Moderate (10-14)
- Moderately Severe (15-19)
- Severe (20-27)

\*Based on scores from 9-item Patient Health Questionnaire (PHQ-9)



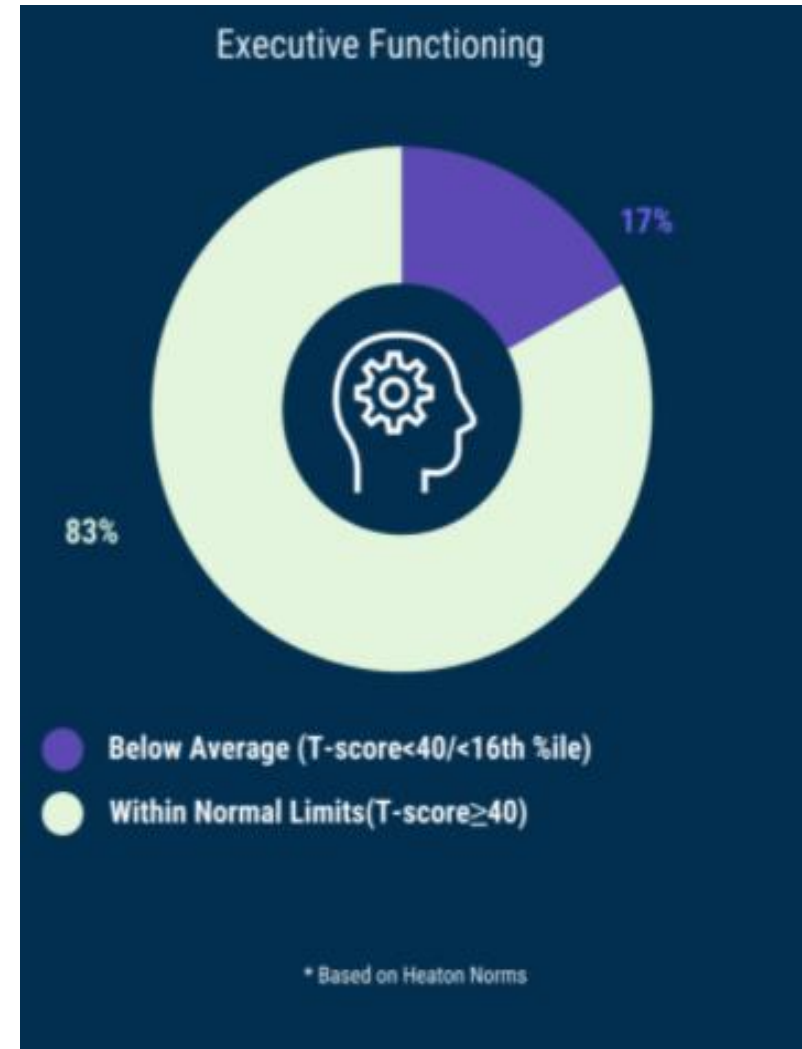
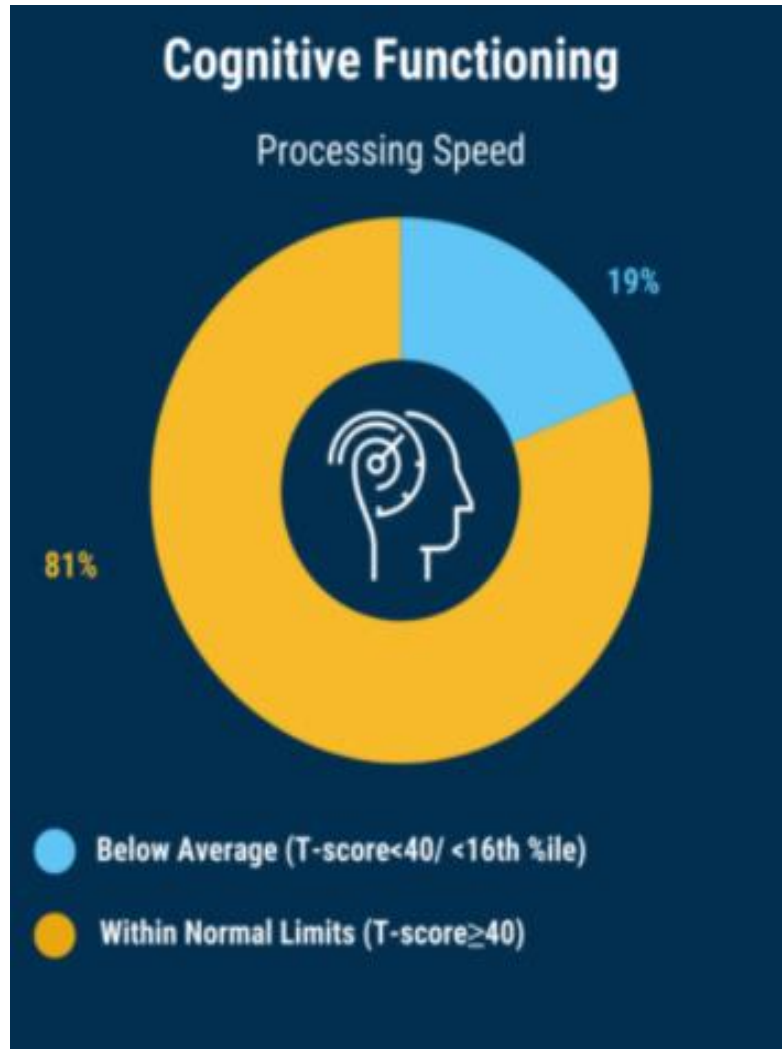
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# LIMBIC-CENC INCLUDES VETERANS WITH A RANGE OF MENTAL AND BRAIN HEALTH DIAGNOSES





# LIMBIC-CENC Collects Rich Longitudinal Data on Each Participant

- Longitudinal assessments occur annually and are of two types: comprehensive in-person evaluations and brief telephone-based evaluations. Program goal is lifelong evaluations and monitoring. Participant retention rate is >82%.
  - Comprehensive assessments require 8 hours of participant time, are completed in one or two days, and are completed at baseline and at 1, 3, 5, 10, 15, 20, and 25 years.
  - Brief telephone assessments require 45 minutes of participant time, are performed at baseline and at all years without a comprehensive evaluations (i.e., Years 2, 4, 6, 7, 8, 9, 11, 12, 13, 14, 16, etc.).
- While one-time assessments are useful, the true strength of LIMBIC-CENC data are the repeated measures over time to assess change (worsening, improvement) and the multimodal nature of testing to establish a personalized “fingerprint” of each participant.

# LIMBIC-CENC Collects Rich Longitudinal Data on Each Participant

- Questionnaires and Diagnostic Testing
  - Alcohol use
  - Pain intensity
  - PTSD symptom severity
  - Depression
  - Parkinson's Disease
  - Quality of Life Scale
  - Brain Injury Symptoms
- Neurophysiology
  - Electroencephalograms (EEGs) and Event-related potentials
  - Computerized Balance testing
  - Computerized Eye Tracking, Hearing Audiograms, Smell Testing
- Genetic testing with DNA extraction, genotyping and genome-wide association studies (GWAS)

# LIMBIC-CENC Collects Rich Longitudinal Data on Each Participant

- NeuroImaging – Images are obtained at each in-person follow-up. 3T MRI scanners are harmonized across all 11 testing sites.
- Blood and Biofluid Biomarkers – Fluids are collected at each in-person follow-up. Measure neurodegenerative and neuroinflammatory proteins associated with dementia or behavioral health conditions.
- Data measures employed are the gold standards for each condition, are uniformly collected and curated, and are entered in a de-identified manner into FITBIR quarterly.
- Aligned with other consortia:
  - Alzheimer's Disease Neuroimaging Initiative (ADNI) studies
  - Transforming Research and Clinical Knowledge in TBI (TRACK-TBI)

# LIMBIC-CENC Data are Entered into FITBIR

- FITBIR is the Federal Interagency Traumatic Brain Injury Research Informatics System ([www.fitbir.nih.gov](http://www.fitbir.nih.gov)) that is currently funded by DoD and NIH.
- A portion of all LIMBIC-CENC data are available for download by registered researchers across the U.S.
  - Some data files are too large for practical download (raw images)
  - Some data are restricted due to protected health information (PHI; date of TBI)
  - Some data are limited by FITBIR data entry fields (biofluids, eye tracking)
  - Most data across different studies must be harmonized
  - Many analyses required support from original researchers to complete
- VA is working with NIH and DoD to ensure that more complete data can be made available

# LIMBIC-CENC FITBIR Contributions

- LIMBIC-CENC Longitudinal Study contributes **96** different forms to FITBIR *[see Addendum for specific elements]*.
- Largest longitudinally/serially collected, brain health dataset in FITBIR. Can be used to see early indicators of degeneration or new mental health conditions.
- As of August 2021, data have been submitted into FITBIR for a total of **1,624** current and former Service Members participants enrolled in the Longitudinal Study.
  - **264,765** total data points
  - **6,451** MRI scans
- LIMBIC-CENC has a formal research sharing policy that encourages “non-LIMBIC researchers” to access all data in collaboration with our research team.



# Active LIMBIC-CENC Collaborations

- Harvard Football Players Health Study
- TRACK-TBI/TED
- NCAA CARE
- CONNECT-TBI
- NIH CDE committees
- Emory University
- NIDILRR TBI Model Systems
- Million Veterans Program
- Concussion Legacy Foundation
- DoD TBI-CoE
- UPENN
- University of Utah
- ENIGMA
- UPMC
- InTBIR



# LIMBIC-CENC Knowledge Translation Center



Long-Term Impact of Military-Relevant Brain Injury Consortium  
Chronic Effects of Neurotrauma Consortium

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ABOUT

FOR SERVICE MEMBERS, VETERANS, AND THE PUBLIC

FOR SCIENTISTS AND CLINICIANS

KNOWLEDGE TRANSLATION CENTER

LIMBIC-CENC Prospective  
Longitudinal Study Data at  
a Glance

LIMBIC-CENC Publication  
Database

LIMBIC-CENC Dementia  
Prognostic Tool

Clinical Pearls

LIMBIC-CENC Assessment  
Tools

LIMBIC-CENC Presentations

Online, Self-Paced Course

Plain Language Abstracts

Postcards

## Knowledge Translation Center

The LIMBIC-CENC knowledge Translation Center makes research findings practical and useful, and gets them to the people who need them. We have made research products about TBI for Veterans, Service Members, clinicians and the public.



- [Postcards](#) use everyday language to present LIMBIC-CENC study's main findings
- [Plain Language Abstracts](#) are the everyday language versions of LIMBIC-CENC publication abstracts by topic
- Our [Online, Self-Paced Course](#), provides brief (about 5 minute) visual and audio presentations on LIMBIC-CENC research. The course covers topic such as aging with TBI risk factors, pain, etc.

<https://www.limbic-cenc.org/index.php/knowledge-translation-center/data-at-a-glance/> [Pearls](#) (BLUF) offer research-based suggestions to apply in practice.



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# LIMBIC-CENC Next Steps

- Recruit and follow 3,000+ service members and Veterans with/without polytrauma (TBI, mental health, pain) and identify patterns of recovery or decline that can be used to tailor care and predict future needs.
- Use mega-dataset of 2.5 million unique service members and Veterans to identify patterns of long-term difficulty (e.g., disability, co-morbid disease, dementia) that can inform research interventions and clinical care aimed at slowing or reversing the course of these disorders.
- Provide real-world information and guidance to clinicians, patients and families that can help to them deal with TBI/Polytrauma-related issues and enhance the quality of Veteran's health.
- Collaborate with researchers across the US/world to leverage findings from a wide range of studies and accelerate discovery and translation.

# LIMBIC-CENC: Getting It Done

LIMBIC 2013 - 2024: 75+ researchers; 19 Universities, 16 VAMCs and 8 DoD facilities



**8** YEARS OF  
LEADERSHIP

**2.5 Million**  
unique records



VA-DoD Mega-  
Database of  
Federal Datasets

**10** COMPLETED  
STUDIES



**200+** PUBLICATIONS



**12** Additional  
Grants Funded



**8** ACTIVE STUDIES

**Longitudinal Study**



**23** SITES  
1,776 SUBJECTS  
(Target = 3,000)



**FITBIR**  
Largest Veteran TBI  
Data Entry



KNOWLEDGE TRANSLATION  
Special Issue on TBI and  
Cognitive Decline



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**Thank you for your attention.  
We look forward to the discussion.**

**WWW.LIMBIC-CENC.ORG**

# Addendum: FITBIR-Specific Data Submission Elements

# LIMBIC-CENC Clinical Data Elements submitted to FITBIR

<i>Study Participation</i>	
Consent	
Study Eligibility	
Protocol Deviation	
Visit details (i.e., missed visit, remote visit)	
Adverse Event	
End of Study (Study withdrawal details)	
<i>Personal Fixed Factors</i>	
Demographics	
Military Status/Military History DVBIC	
TBI Characteristics/Outcomes/Exposure	
Potential Concussive Event Mapping	
Retrospective Concussion Diagnostic Interview - Blast	
Retrospective Concussion Diagnostic Interview - General	
Blast Exposure Threshold Survey	
Glasgow Outcome Scale Extended	
<i>Moderating Factors/Health Behaviors</i>	
Drug Abuse Screening Test-10	
Healthcare Utilization	
Alcohol Use Disorders Test-Consumption	
Deployment Risk and Resiliency Inventory - 2 Combat	
Deployment Risk and Resiliency Inventory - 2 Support	
Behavior Risk Factor Surveillance System	
Abstraction of Service-Connected Disabilities	
TBI Model Systems - Employment Data	
TBI Model Systems Preinjury History	
Medical Symptom Validity Test	



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# LIMBIC-CENC Clinical Data Elements submitted to FITBIR

## *Comorbidities/Psychosocial Functioning*

Neurobehavioral Symptom Inventory-22  
EuroQol Group 5 Dimension 5 Level  
Satisfaction with Life Scale  
Baseline Epilepsy Screening Questionnaire  
Pittsburgh Sleep Quality Index  
Patient Health Questionnaire Depression Scale  
General Self-Efficacy Scale  
Dizziness Handicap Inventory -Screening Version  
Headache Impact Test  
TBI-QOL Ability to Participate in Social Roles and Activities  
TBI-QOL Anger  
TBI-QOL Fatigue  
TBI-QOL Resilience  
TBI-QOL Anxiety  
TBI-QOL Emotional & Behavioral Dyscontrol  
Community Reintegration of Injured Service Members  
Mini International Neuropsychiatric Interview  
PTSD Checklist for DSM-V  
BU Contact Sport History Questionnaire  
Military Training Head Jolt Exposure Questionnaire

## *Neuropsychological Functioning*

Brief Test of Adult Cognition by Telephone  
California Verbal Learning Test-II  
Trail Making Tests Parts A and B  
NIH Toolbox Cognitive Battery  
TBI-QOL Cognition - General Concerns  
TBI-QOL Executive Function  
Brief Visuospatial Memory Test-Revised  
Wechsler Adult Intelligence Scale-4th Edition  
Test of Premorbid Functioning  
Delis-Kaplan Executive Function System  
Clinical Dementia Rating Scale

# LIMBIC-CENC Clinical Data Elements submitted to FITBIR

## *Motor/Movement Performance Tests*

Grooved Pegboard Test

Balance Error Scoring System

Computerized Dynamic Posturography

NIH Toolbox 4-Meter Walk Gait Speed

Unified Parkinson's Disease Rating Scale

## *Physiological/Sensory*

EEG/ERP

Eye Tracking (Eyelink, RightEye)

Brief Smell Identification Test

NIH Toolbox Pain Interference

NIH Toolbox Pain Intensity

TBI-QOL Pain Interference

AntiSaccades

Visual Acuity

Tests for Auditory Processing Disorders (SCAN 3)

Audiometry

Subjective Visual Vertical Test

Vital Signs/Biometrics (HR, BP, BMI)

Hearing Handicap Inventory for Adults, Screening version (HHIA-S)

Tinnitus Functional Index

## *Biomarkers/biofluid*

Apo-E

Neuroendocrine panel (TSH, IGF-1, TSH, Testosterone)

## *Neuroimaging*

MRI Common Data Elements Coding

MRI raw images

# LIMBIC-CENC Clinical Data Elements submitted to FITBIR

- For the Longitudinal Study, the following MRI sequences are submitted:
  - T1-weighted (MPRAGE, SPGR, FSPGR BRAVO)
  - T2-weighted (TSE, T2, CUBE T2, SPC)
  - GRE, T2\* or susceptibility weighted imaging (SWI/SWAN)
  - Fluid attenuated inversion recovery (FLAIR, FLAIR CUBE)
- For single-center studies completed from 2013-2018, the following MRI additional sequences have been submitted:
  - resting state (fMRI)
  - diffusion imaging

# LIMBIC-CENC Clinical Data Elements submitted to FITBIR

- Fluid Biomarkers submitted to FITBIR
  - Neuroendocrine Panel
    - IGF-1 (Growth hormone)
    - TSH (Thyroid hormone)
    - Testosterone (Gonadal hormone)
  - Genomics
    - APOE
- The following Fluid Biomarker research-grade assay results are not submitted to FITBIR, but the list of assays performed under LIMBIC-CENC for sharing with collaborators will be
  - GWAS
  - DNA Methylation
  - MicroRNA
  - Plasma protein studies (tau, NFL, Glial Fibrillary Acidic Protein, UCLH-1)
  - Neuronally derived exosomes
  - Exosome counts
  - Exosomal protein measurements

