LONG-TERM IMPACT OF MILITARY-RELEVANT BRAIN INJURY CONSORTIUM - CHRONIC EFFECTS OF NEUROTRAUMA CONSORTIUM (LIMBIC-CENC)

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BLUF

- Mature, federal mTBI research consortium targeting long-term outcomes with robust infrastructure.
- Since 2013, 12 research studies have been completed with 200+ publications and 12 additional grants funded.
- Currently, supporting 6 active research studies
  - 2,000+ (target 3,000) participant Prospective Longitudinal Study
  - Prospective Biomarker Discovery and Novel Neuroimaging studies
  - 2.5+ million-participant Retrospective Database, Phenotypes and Health Economics big data studies using extant federal datasets
  - Also supporting 2 prospective intervention (sleep, cognitive dysfunction) trials
- Key deliverable: A range of Knowledge Translation products have been developed and additional ones are underway for consumers, family, clinicians and researchers.
Summary of LIMBIC-CENC 2013-2022

- The Chronic Effects of Neurotrauma Consortium (CENC 2013–19) identified a range of differences between SM’s and Veterans with and w/o mild TBI in the 1,700+ participant Prospective Longitudinal Study (PLS).

- CENC derived a unique, combined mega-dataset from the VA and DoD’s electronic medical, benefits, pharmacy and administrative records of 2+ million unique Veterans that revealed linkages between TBI and dementia, Parkinson’s disease, chronic pain and suicide.

- The Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC 2019–24) commenced October 2019 and has grown the PLS to 2,000 (target 3,000) participants and also continues to analyze mega-dataset (2.5 million Veterans)

- LIMBIC-CENC’s research teams have identified an association between TBI and dementia and biofluid markers of repetitive TBI, and confirmed that pain and mental health disorders worsen dysfunction after mTBI.
LIMBIC-CENC Organizational Chart

Leadership Team
- Consortium Director/PI: David Callu, MD
- Associate Consortium Director/Co-PI: COL Kristopher Radcliffe, MD
- External Collaborations Director/Co-PI: CCL. (Q) Sidney Hind, MD
- Associate Consortium Director/Co-PI: Kristine Yaffe, MD

Coordinator Director: Kevin Sickinger

Biomarkers
- Kim Kenney, MD
- Jessica Gill, PhD

Novel Neuroimaging Study
- Wildes

Prospective Longitudinal Study
- Walker

Research Studies
- Retrospective Database Study
  (Suffolks)
- Health Economics Study
  (Comstock)
- Phenotypes Study
  (Pugh)

Core Facilities
- Data and Biostatistics
  (Guyenem, PhD)
- Mary Jo Pugh, PhD
- Neuroimaging
  (Elisabeth Wilde, PhD)

11 Clinical Study Sites
- DoD
- VA
- DoD/VA

Aggregated VA and DoD Database

Regulatory OverSite
- HIPPO-VA/HIP-IRB of Records

Department of Defense
- Government Steering Committee
- Department of Veterans Affairs

Study Consort Diagram for PLS Initial Evaluations

Screened (N=4,690) → Not eligible (N=2,686)

Consented (N=2,004) → Not eligible: 40

Enrolled (as of 09/30/2021) (N=1,964)

- No mTBI Exposure Withdrawn prior to complete baseline (N=14)
- Ongoing (N=17)

Complete Baseline and Progress to Follow-up (N=1,847)*

- mTBI Exposure Withdrawn prior to complete baseline (N=86)

*As of Sep 30, 2021

- Proportion with mTBI(s): 82%
- Median (IQR) # of mTBIs per person: 2 (1,3)
Comparison of Accrued Study Cohort to OEF/OIF Population

Limbic cohort is highly representative of the overall OEF/OIF cohort that we have been tasked to study.

Limbic-CENC Cohort

- Male
- Officer
- Medical Status
- White
- Alcohol Low Risk
- Non-Prescription Drug Use
- Married

Limbic-CENC Biomarker Core

- Collated, stored, processed and aliquoted biospecimens from 1,859 Study 1 (426 f/u) participants and 163 samples from previous CENC studies for current total 28,223 aliquots of in the biorepository available for analysis.

- 4,202 have been distributed to LIMBIC Biomarker Discovery projects and to 3 collaborative projects approved by Research Committee.
Creation of a Dashboard to Compare DoD, VA and Private Sector Inpatient Costs by Diagnosis Related Groups (DRG)

- Created a cohort of Veterans diagnosed with TBI in inpatient or outpatient VA administrative data based on DoD/VA ICD-9 codes between 2000-2015.

- Requested DoD data for those veterans who have records in DaVINCI.

- Followed utilization and cost of inpatient care in DoD Tricare and VA between 2004-2020 based on DRGs.

- For all inpatient discharges in DoD Tricare and VA 2004-2020, estimated the median DoD billing amount and VA MCA cost per TBI non-surgical DRG.

- Used AHRQ, Health Care Utilization Project (HCUP) National Inpatient Sample (NIS) tool to calculate the median private sector hospital charge and hospital cost by TBI non-surgical DRG for 2017.

- Used the US Department of Labor Inflation Calculator to convert $ to 2/2021 value.

Progress: LIMBIC-CENC Database

- Expanded and updated through 2020

- Contains inpatient/outpatient diagnosis codes and medication data for all 2.5 million Veterans, for use in defining outcomes, comorbidities, and examining treatment

- TBI and TBI severity defined using Defense and Veterans Brain Injury Center (DVBIC) definitions for TBI case detection

- TBI severity: 82% Mild, 17% Moderate, and 1% Severe/Penetrating
TBI and Risk of Sleep Disorders in Nearly 200,000 US Veterans

- Veterans with TBI were 41% more likely to develop any sleep disorder, adjusting for demographics and medical and psychiatric conditions: HR=1.41 (1.37-1.44)

- Veterans with TBI were more likely to develop:
  - Sleep apnea HR=1.28 (1.24-1.32)
  - Insomnia HR=1.50 (1.45-1.55)
  - Hypersomnia HR=1.50 (1.39-1.61)
  - Sleep-related movement disorders HR=1.33 (1.16-1.52)

Leng et al., *Neurology*, 2021

Progress: TBI, Cardiovascular Disease, and Risk of Dementia among Older US Veterans

- CVD and TBI are both important risk factors for dementia; however, little is known about how they interact on this risk

- Age, sex, and race-matched sample of Veterans aged 55+ with and without TBI (mean age=67 years), with no dementia at baseline
  - N=195,416 per group
  - At least 1 year of follow-up; average=6.6 years

- Preliminary Results:
  CVD and CV risk factors are 2X higher in people with TBI
  - TBI only: HR=2.35 (2.26-2.43)
  - CVD only: HR=1.26 (1.20-1.33)
  - TBI + CVD: HR=2.83 (2.72-2.94)
  Additive effect between TBI and CVD; no interaction

Kornblith et al., *in progress*
LIMBIC Key Findings 2021

- Veterans with TBI have higher rates of dementia, pain, opioid usage, mental health diagnoses, cardiovascular disease, stroke, and sleep dysfunction.

- Service members and veterans with mTBI or blast do NOT have increased rates of neuroendocrine dysfunction.

- Tau and p-tau levels increased by number of blast exposures in Combat-exposed service members and veterans with mTBI.

- In service members and veterans, a greater # of mTBIs (3+) is associated with increased symptom burden and serum NFL levels.

- In service members and veterans, increased “brain age” by imaging associated with increased h/o combat mTBI, # mTBI’s, depression, PTSD, poor sleep.
Brain Injury Special Edition – February 2022

- Practical Approaches to Assessing and Mitigating the Risk of Cognitive Decline after Concussion: Findings from the Long-term Impact of Military-relevant Brain Injury Consortium (LIMBIC)
  1. Relationship of Advanced Neuroimaging Findings to Symptom Burden and Dementia Risk after Concussion
  2. Relationship of Fluid Biomarker Findings to Symptom Burden and Dementia Risk after Concussion
  3. Role of Physical Activity following Combat-related Concussion in Impacting Dementia Risk
  4. Association of TBI History and Dementia in Veterans: A Mega-Database Analysis
  5. Clinical Phenotypes of Post-TBI Symptoms and Risk for Dementia
  6. Sleep disorders in TBI patients: potential new targets for reducing dementia risk
  7. Health Economics of Concussion, TBI and Dementia
  8. The Role of Transcranial Magnetic Stimulation in Post-Traumatic Cognitive Dysfunction
  9. Impact of PTSD on Symptom Burden and Dementia Risk After Concussion

- Supporting Resources from KTC for each topic area: Consumer Knowledge Cards, Lay Person Abstracts, Clinical and Research Pearls, Podcast
LIMBIC Roadmap – 2013-2021

Describe the Common Effects after mTBI

<table>
<thead>
<tr>
<th>Area</th>
<th>Contributing Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosensory Vision Hearing Vestibular</td>
<td>• Described in 5 completed CENIC projects (Aiken, MacDonald, Kardon, Yaffe, Walker)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in 3 active LIMBIC studies (Walker, Yaffe, Pugh)</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>• Described in 1 completed LIMBIC study (Walker, Kenney)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in 1 active LIMBIC study with LIMBIC (Walker)</td>
</tr>
<tr>
<td>Sleep</td>
<td>• Described in 1 completed CENIC project (Jax, MacDonald, Jax, Yaffe, Walker)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in TBI/IBI collaboration study with LIMBIC (Richardson, Dismuke)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in 2 LIMBIC studies (Werner, Richardson, Kenney, Wilde)</td>
</tr>
<tr>
<td>Pain</td>
<td>• Described in 4 completed CENIC projects (MacDonald, Taber, Yaffe, Walker)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in 2 active LIMBIC studies (Walker, Yaffe, Pugh)</td>
</tr>
<tr>
<td>Cognitive</td>
<td>• Described in 3 completed CENIC projects (Mufson, Crawford, MacDonald, Taber, Yaffe, Walker)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in all active LIMBIC studies (Wilde, Kenney, Yaffe, Walker, Pugh, Dismuke)</td>
</tr>
<tr>
<td></td>
<td>• Fall 2021 Brain injury special issue dedicated to risks for cognitive decline after TBI</td>
</tr>
<tr>
<td>Psychological</td>
<td>• Described in 3 completed CENIC projects (Jax, MacDonald, Taber, Yaffe, Walker)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in 1 active LIMBIC studies (Walker, Yaffe, Pugh, Dismuke)</td>
</tr>
<tr>
<td>Neurological</td>
<td>• Described in 6 completed CENIC projects (Mufson, Crawford, MacDonald, Yaffe, Taber, Jax, Walker)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in 2 active LIMBIC studies (Walker, Yaffe, Pugh, Dismuke)</td>
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Define the Association Between mTBI, Symptom Burden And Neurodegeneration

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<tr>
<th>Area</th>
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</thead>
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<tr>
<td>Symptom Burden</td>
<td>• Described in 7 completed CENIC projects (Aiken, MacDonald, Yaffe, Taber, Jax, Mufson, Crawford, Walker)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in 4 active LIMBIC studies (Walker, Pugh, Yaffe, Dismuke)</td>
</tr>
<tr>
<td>Neurodegeneration</td>
<td>• Described in 6 completed CENIC projects (MacDonald, Yaffe, Taber, Jax, Mufson, Crawford, Walker)</td>
</tr>
<tr>
<td></td>
<td>• Being addressed in 6 active LIMBIC studies (Walker, Pugh, Yaffe, Dismuke, Wilde, Kenney)</td>
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<td></td>
<td>• Fall 2021 Brain injury special issue and knowledge translation products dedicated to risks for cognitive decline after TBI (Cifu, Hinds, Seal)</td>
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LIMBIC Roadmap – The Journey Ahead 2021-2024 (and Beyond)

Define and Disseminate Tools to Diagnosis and Prognosticate Symptom Burden and Neurodegeneration

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<th>Research Question</th>
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<tr>
<td>Symptom Burden</td>
<td>• Described in 8 completed CENIC projects (Wilde, MacDonald, Yaffe, Taber, Jax, Davenport, Aiken, Walker)</td>
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<tr>
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<td>• Being addressed in 6 active LIMBIC studies (Walker, Pugh, Kenney, Wilde, Dismuke, Yaffe)</td>
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<tr>
<td></td>
<td>• Knowledge Translation Core developing suite of tools (Seel, Hinds)</td>
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<tr>
<td></td>
<td>• KTC Risk Assessment Tool linked with Amelioration Strategies (Seel)</td>
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<tr>
<td></td>
<td>• Completed TMS for cognitive deficits after mTBI at LIMBIC site (Manning)**</td>
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<td></td>
<td>• Examining sleep interventions to reduce cognitive symptoms (Werner)**</td>
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<tr>
<td></td>
<td>• Collaborating with VA/CSP Neuroendocrine Assessment and Intervention trial across nine LIMBIC VA sites (Walker)**</td>
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<tr>
<td>Neurodegeneration</td>
<td>• Described in 8 completed CENIC projects (Wilde, MacDonald, Yaffe, Taber, Jax, Davenport, Walker, Mufson, Crawford)</td>
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Next Steps: Interventions 2024-2029

• Continue Active Research applying interventions:
  • Multiple LIMBIC collaborators with additional grant funding to study mTBI interventions
• Partner with other investigators to leverage LIMBIC PLS site infrastructure and participants for intervention trials
• Mentor and Support next generation of TBI researchers
  • Co-Investigators on LIMBIC projects
  • Mentors on CD4/4K-award grants
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Questions