

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

PRESENTED AT LUDWIG-MAXIMILIANS-UNIVERSITÄT
MÜNCHEN

Sidney R. Hinds II, MD, FAAN
6 July 2019



Disclaimers and Disclosures

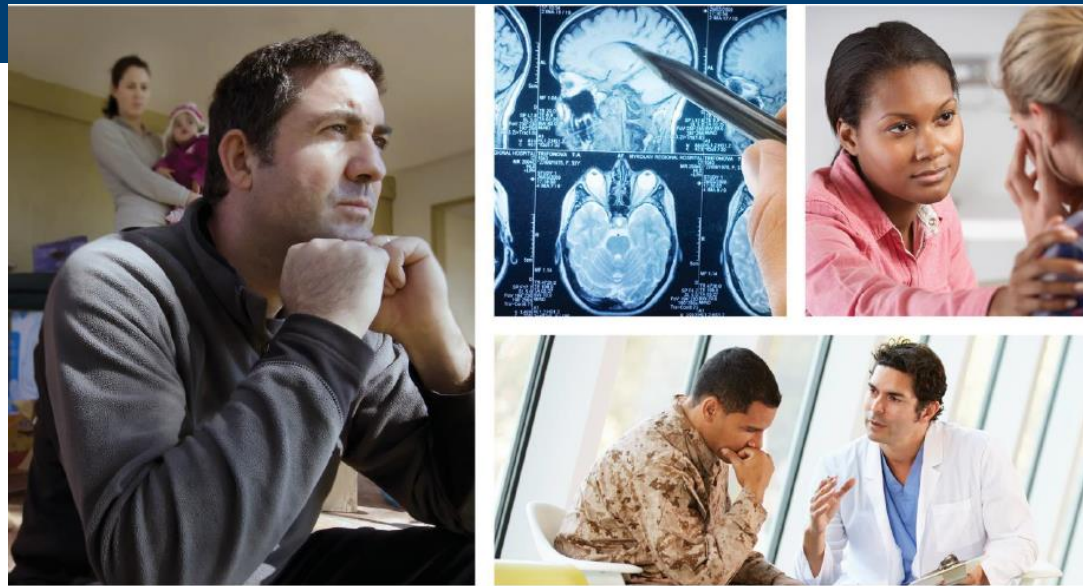
- The opinions and assertions contained herein are the private views of the author and are not to be construed as official or reflecting the views of the United States Medical Research and Development Command (USAMRDC), the United States Army Futures Command (USAFC), the Department of the Army or the Department of Defense.
- I have no financial relationships or conflicts of interest to disclose
- I am a non-funded Co-Principal investigator for The Chronic Effects of Neurotrauma Consortium (CENC)/Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) and the Post-traumatic Headache Clinical Recommendation Headache Research Study

Goals

- Provide an overview of the Chronic Effects of Neurotrauma Consortium (CENC)
- Provide a glimpse into some of the accomplishments of CENC
- Provide some insight into Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC)



U.S. Air Force Photo by Master Sgt. John Nimmo, Sr.



National Research Action Plan

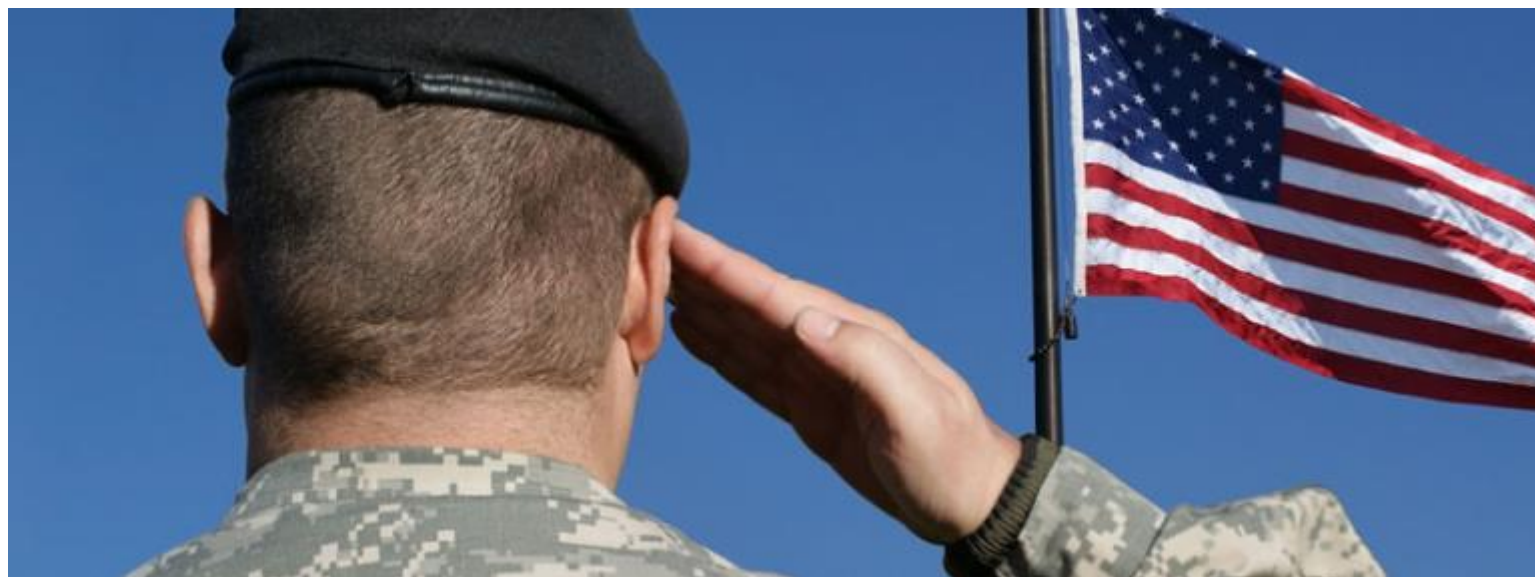
Responding to the Executive Order
*Improving Access to Mental Health
Services for Veterans, Service Members,
and Military Families (August 31, 2012)*

Department of Defense
Department of Veterans Affairs
Department of Health and Human Services
Department of Education

August 2013



THEN



Dr. David Cifu



Dr. Ramon
Diaz-Arrastia



Dr. Rick Williams





CENC Sites

Barrows Neurological Institute, Phoenix, AZ

Baylor College of Medicine, Houston, TX

Boston University, Boston, MA

Duke University School of Medicine,
Durham, NC

Fort Belvoir Community Hospital,
Alexandria, VA

Hunter Holmes McGuire VA, Richmond, VA

James A. Haley Veterans Hospital,
Tampa, FL

Iowa City VA Health Care Center

Medical College of Wisconsin,
Milwaukee, WI

Michael E. DeBakey VA Medical Center,
Houston, TX

Milwaukee VA Medical Center,
Milwaukee, WI

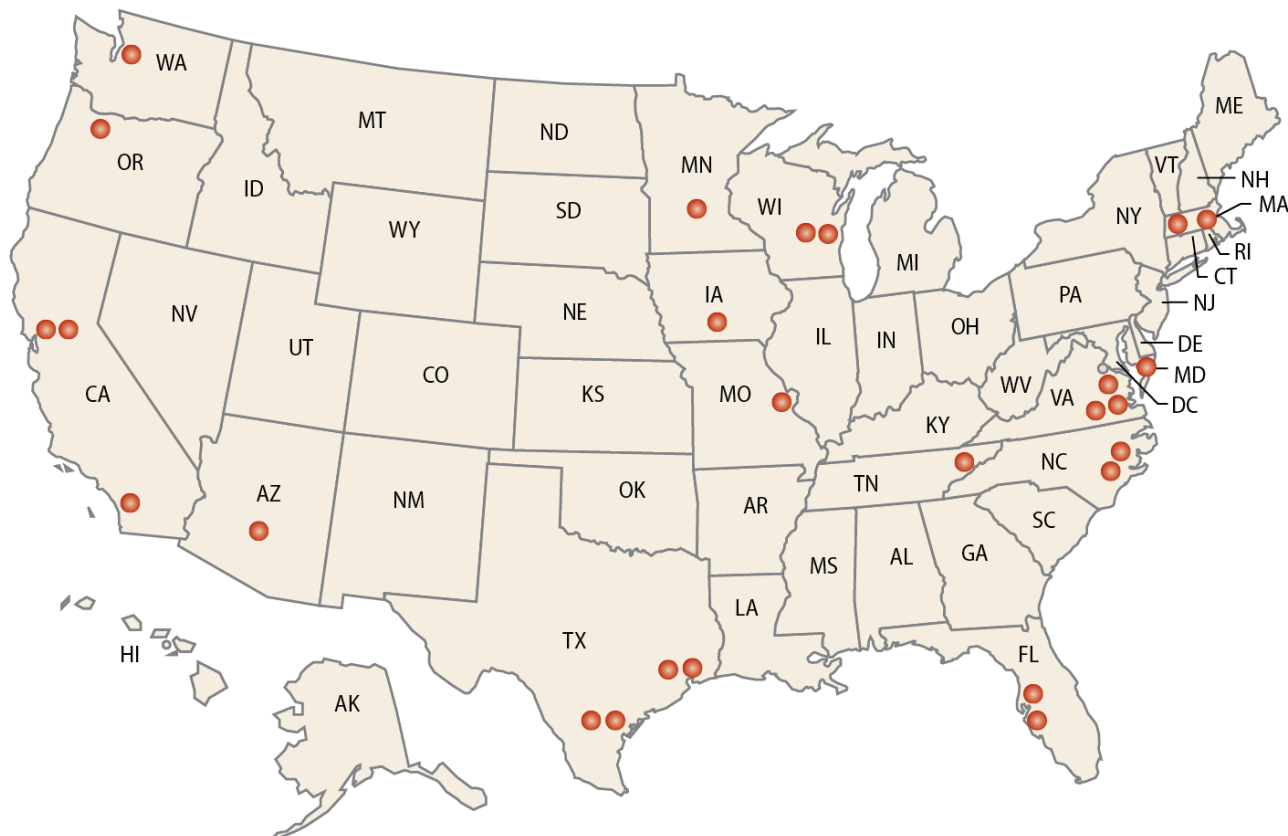
Minneapolis VA Health Care System

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, St Louis, MO

University of Washington, Seattle, WA

VA Boston Healthcare System

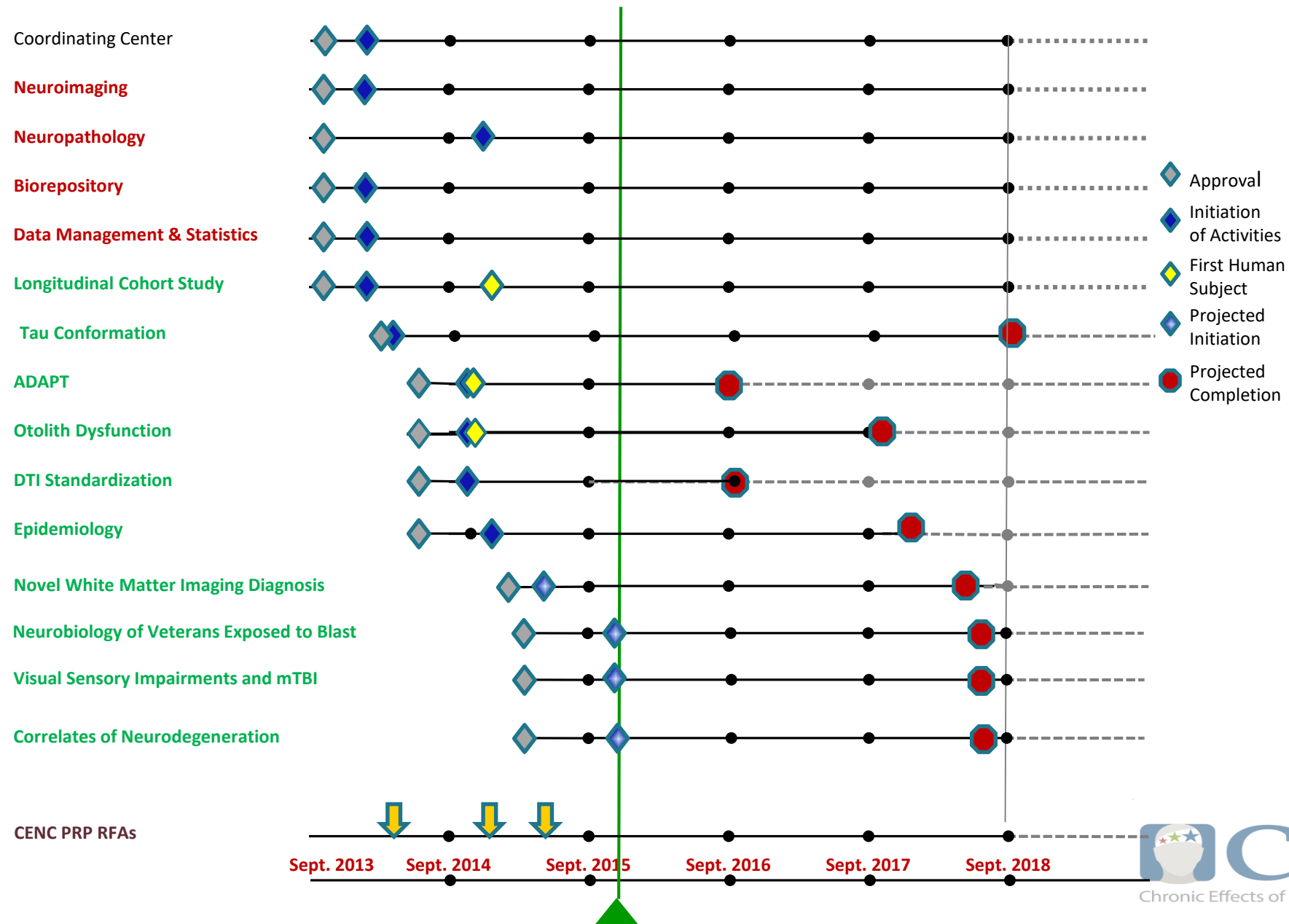
VA Portland Health Care System

VA San Diego Health Care System, San Diego, CA

Virginia Commonwealth University, Richmond, VA



CENC Cores & Studies Timeline



CENC Roadmap

Describe the common effects after mTBI

Research Question	Contributing Studies
Neurosensory Vision Hearing Vestibular	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Otolith Dysfunction and Postural Stability (Aiken) Visual Sensory Impairments and Progression Following Mild Traumatic Brain Injury (Kardon)
Neuroendocrine	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe)
Seizures	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe)
Sleep	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Novel White Matter Imaging to Improve Diagnosis of mTBI (Jak) Structural & Functional Neurobiology of Veterans Exposed to Blast Effects (Taber)
Pain	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Structural & Functional Neurobiology of Veterans Exposed to Blast Effects (Taber)
Cognitive	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Basic Science Tau Modification Study (Mufson/Crawford) Structural & Functional Neurobiology of Veterans Exposed to Blast Effects (Taber)
Psychological	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Novel White Matter Imaging to Improve Diagnosis of mTBI (Jak) Structural & Functional Neurobiology of Veterans Exposed to Blast Effects (Taber)
Neurologic	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Basic Science Tau Modification Study (Mufson/Crawford) Novel White Matter Imaging to Improve Diagnosis of mTBI (Jak) Structural & Functional Neurobiology of Veterans Exposed to Blast Effects (Taber)

Define association between mTBI, common effects and neurodegeneration

Research Question	Contributing Studies
mTBI and Common Effects	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Basic Science Tau Modification Study (Mufson/Crawford) Otolith Dysfunction and Postural Stability (Akin) Novel White Matter Imaging to Improve Diagnosis of mTBI (Jak) Structural & Functional Neurobiology of Veterans Exposed to Blast Effects (Taber)
mTBI and Neurodegeneration	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Basic Science Tau Modification Study (Mufson/Crawford) Novel White Matter Imaging to Improve Diagnosis of mTBI (Jak) Structural & Functional Neurobiology of Veterans Exposed to Blast Effects (Taber)



CENC Roadmap cont.

Identify tools to measure the diagnosis and prognosis for common effects and neurodegeneration

Research Question	Contributing Studies
Tools to Diagnose and Prognosticate Common Effects after mTBI	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Otolith Dysfunction and Postural Stability (Akins) Diffusion Tensor Imaging Standardization Using Novel MR Diffusion Phantoms (Wilde) Novel White Matter Imaging to Improve Diagnosis of mTBI (Jak) Structural & Functional Neurobiology of Veterans Exposed to Blast Effects (Taber) Visual Sensory Impairments and Progression Following Mild Traumatic Brain Injury (Kardon) Clinical and neuroimaging correlates of neurodegeneration in military mTBI (Davenport)
Tools to Diagnose and Prognosticate Common Neurodegeneration after mTBI	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Epidemiology of mTBI and Neurosensory Outcomes (Yaffe) Basic Science Tau Modification Study (Mufson/Crawford) Diffusion Tensor Imaging Standardization Using Novel MR Diffusion Phantoms (Wilde) Novel White Matter Imaging to Improve Diagnosis of mTBI (Jak) Structural & Functional Neurobiology of Veterans Exposed to Blast Effects (Taber) Clinical and neuroimaging correlates of neurodegeneration in military mTBI (Davenport) Visual Sensory Impairments and Progression Following Mild Traumatic Brain Injury (Kardon)



Assess the efficacy of intervention for common effects and neurodegeneration after mTBI

Research Question	Contributing Studies
Assess Interventions for Neurosensory Common Effects	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald) Otolith Dysfunction and Postural Stability (Akins)
Assess Interventions for Other Common Effects	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald)
Assess Interventions for Neurodegeneration	<ul style="list-style-type: none"> Observational Study on Late Neurologic Effects of OEF/OIF/OND Combat (Cifu) Assessment of Long-Term Outcome and Disability in Active-Duty Military Prospectively Examined Following Concussive TBI (MacDonald)

LONGITUDINAL COHORT STUDY

PI: Dr. William Walker



EPIDEMIOLOGY STUDY

a retrospective cohort study integrating existing federal healthcare **databases** to study the **chronic effects** of mTBI on neurodegenerative disease and other comorbidities, and the methods to treat and rehabilitate adverse effects of mTBI in Veterans over time.

Kristine Yaffe, M.D.

Mary Jo Pugh, Ph.D.

Tau Modifications Study

a basic science project to identify the key molecular events in the processing of tau after TBI in **rodents** and **humans**, with the goal of developing novel biomarker tools to assess tau dysregulation after TBI.

Fiona Crawford, Ph.D.
Elliott Mufson, Ph.D.

OTOLITH DYSFUNCTION AND POSTURAL STABILITY

a prospective case-controlled study to determine the effect of **inner ear (vestibular) dysfunction** on balance, gait and quality of life in Veterans.

Faith Akin, Ph.D.

Courtney Hall, PT, Ph.D.

NOVEL WHITE MATTER IMAGING TO IMPROVE DIAGNOSIS OF MTBI STUDY

an observational cohort study assessing the diagnostic utility of **multicomponent-driven equilibrium single pulse observation of T1 and T2 (mcDESPOT)** on brain volume after mTBI in Veterans with a history of mTBI, posttraumatic stress or both.

Amy Jak, Ph.D.

ADAPT/EVOLVE STUDY

a follow up to an existing prospective case-controlled study of **advanced MR** imaging and clinical outcomes measures **3-5 years** after concussive traumatic brain injury (TBI) in US military personnel injured during deployment.

Christine MacDonald, Ph.D.

Structural and Functional Neurobiology of Veterans Exposed to Primary Blast Forces Study

an observational cohort study designed to investigate the microstructural nature and functional effect of diffuse heterogeneous white matter abnormalities following mTBI in Veterans of recent conflicts, using advanced multimodal neuroimaging, **structured interview**, cognitive testing and **questionnaires**.

Katherine Taber, Ph.D.

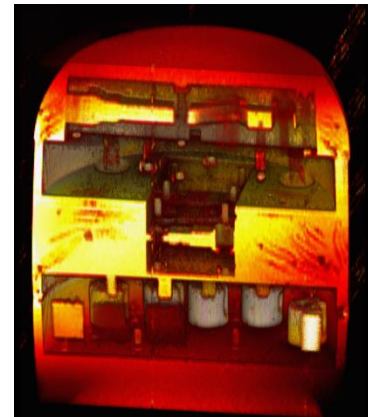
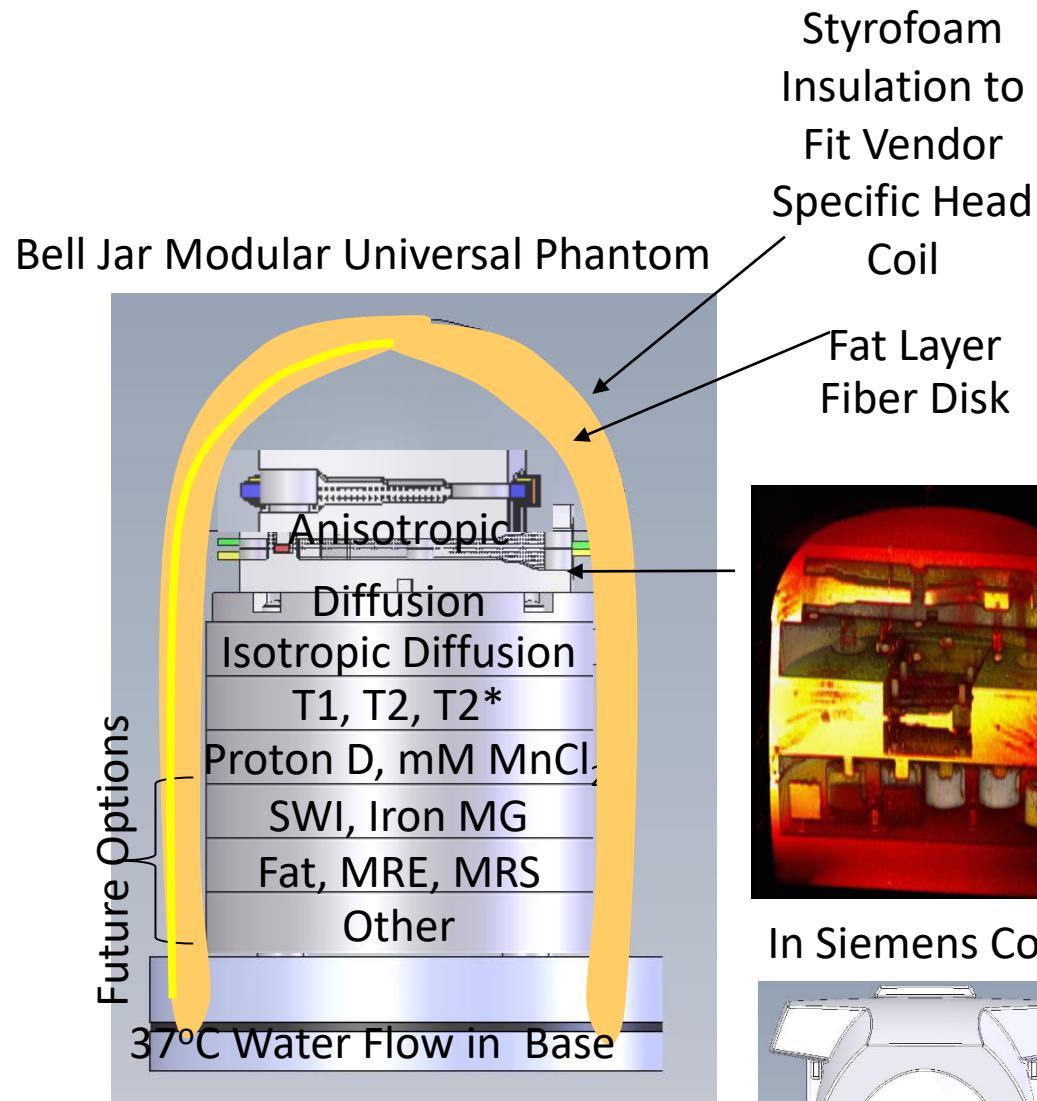
DIFFUSION TENSOR IMAGING STANDARDIZATION USING NOVEL MR DIFFUSION PHANTOMS

an observational study to cross-validate the many **different scanners** across the VA hospital system to provide the same imaging information in suspected cases of TBI

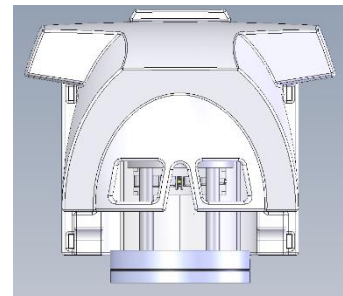
Elisabeth Wilde, Ph.D.

James Provenzale, Ph.D.





In Siemens Coil



CLINICAL AND NEUROIMAGING CORRELATES OF NEURODEGENERATION IN MILITARY MTBI STUDY

an observational cohort study designed to test potential markers of mTBI and assess self-report measures by re-assessing an existing cohort of Veterans and Service Members by collecting data through **clinical interviews, self-reporting measures, neuroimaging** and blood-based protein expression.

Nicholas Davenport Ph.D.

VISUAL SENSORY IMPAIRMENTS AND PROGRESSION FOLLOWING MTBI

an observational cohort study to identify the spectrum of **visual sensory disturbances** after mTBI using a **new imaging technology**, and further to identify potential therapeutic modalities including focal transcranial magnetic stimulation, visual behavioral tasks that may strengthen synaptic connections, chemical neuromodulation, and peripheral and central nerve stimulation.

Randy Kardon, M.D., PH.D.

Glenn Cockerham, M.D.

Kelvin Limm, M.D.

NOW



CENC-LIMBIC program (5-year, \$50 million renewal)

- Expand Prospective Study cohort to 3,000+ participants from all military eras across 11 recruitment sites, followed annually and comprehensively re-evaluated every 5 years.
- Extend Retrospective Study of 2 million unique Veterans to assess TBI-related risks for ongoing symptoms and neurodegenerative conditions and study health economics and clinical utilization of mTBI

LIMBIC Cores

Coordinating Center

- Virginia Commonwealth University, Richmond, VA

Imaging Core

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

Clinical Studies Core

- Virginia Commonwealth University, Richmond, VA

Biomarkers Core

- Uniformed Services University of the Health Sciences, Bethesda, MD

Data and Biostatistics Core

- Hunter Holmes McGuire VA/Virginia Commonwealth University, Richmond, VA
- VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT

LIMBIC Studies

Prospective Longitudinal Study Enrollment Sites

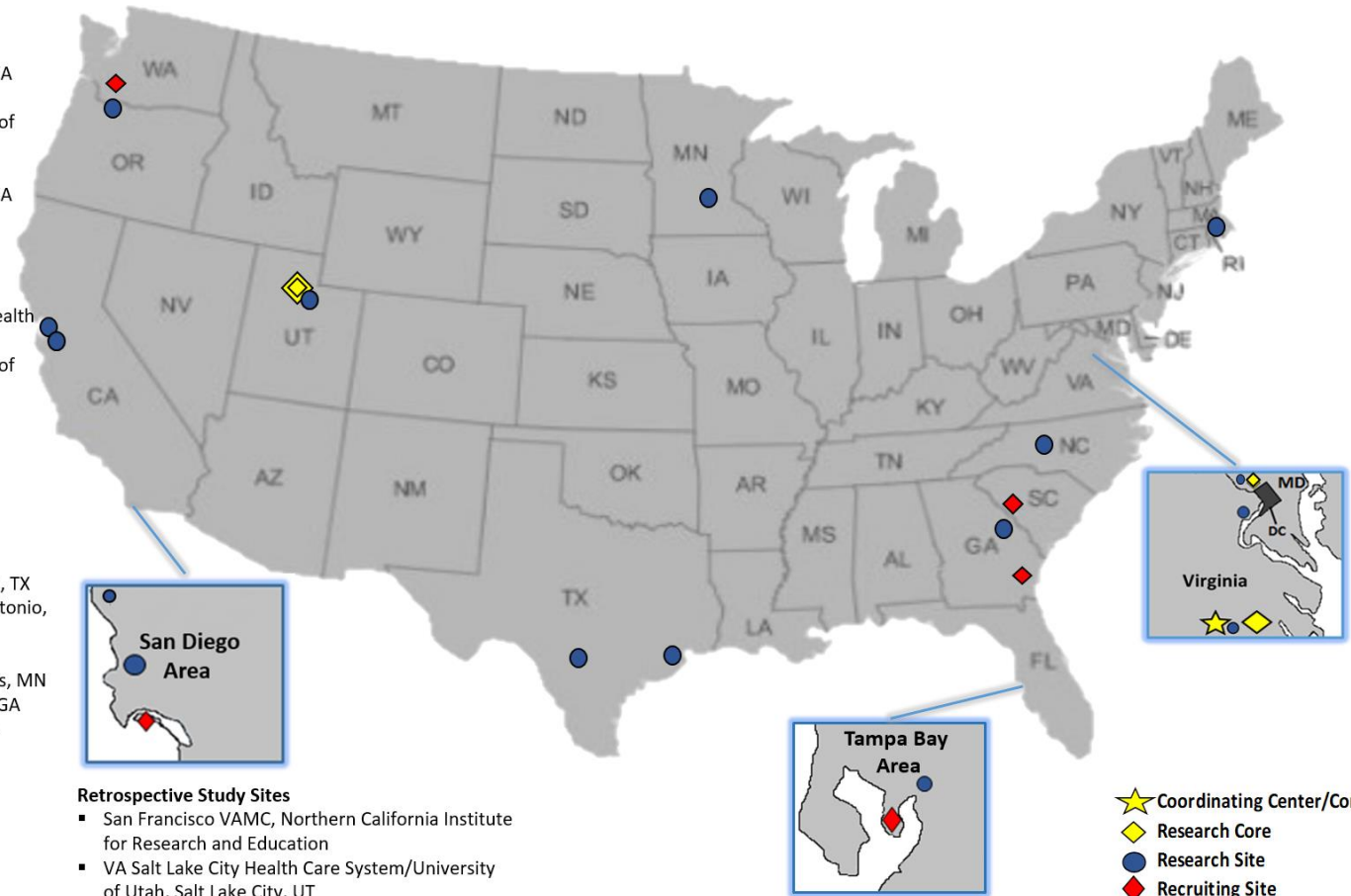
- Hunter Holmes McGuire VA, Richmond, VA
- James A. Haley Veterans Hospital, Tampa, FL
- VA Boston Healthcare System, Boston, MA
- VA Portland Health Care System, Portland, OR
- Michael E. DeBakey VA Medical Center, Houston, TX
- South Texas Veterans Healthcare Center, San Antonio, TX
- WG Hefner VA Medical Center, Salisbury, NC
- Minneapolis VA Health Care System, Minneapolis, MN
- Eisenhower Army Medical Center, Fort Gordon, GA
- Fort Belvoir Community Hospital, Alexandria, VA
- VA San Diego Health System/University of California/Camp Pendleton, CA

Prospective Longitudinal Study Recruiting Sites

- Joint Base Lewis-McChord, WA
- MacDill Air Force Base, FL
- Fort Stewart, GA
- Fort Jackson, SC
- Navy Base Coronado, CA

Retrospective Study Sites

- San Francisco VAMC, Northern California Institute for Research and Education
- VA Salt Lake City Health Care System/University of Utah, Salt Lake City, UT
- Uniformed Services University of the Health Sciences, Bethesda, MD
- VA Palo Alto Health Care System



CENC STUDY #1: MULTICENTER LONGITUDINAL STUDY OF LATE NEUROLOGIC EFFECTS OF COMBAT EXPOSURE AND MILD TBI

William C. Walker, MD



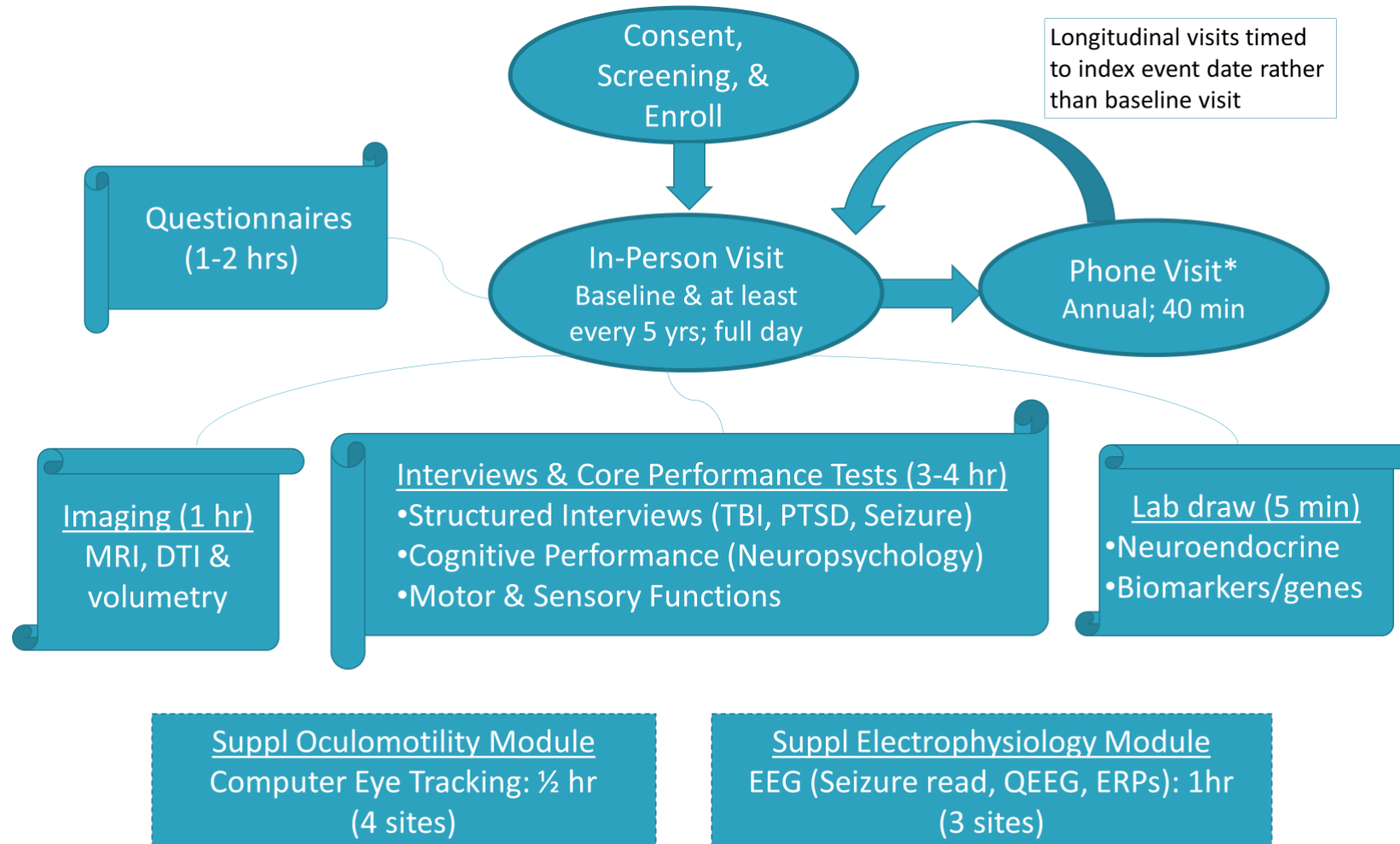
CENC Study 1 Main Overall Goal & Significance

- Goal: Establish a large, geographically dispersed, research cohort of combat exposed OEF/OIF/OND era military persons with and without prior mTBI, and measure their chronic sequelae and comorbidities

Significance (so what?):

- By establishing the cohort, mapping out their lifetime concussion histories, and performing comprehensive and longitudinal assessments, this study will:
 - **Answer the important questions about risk factors for and vulnerability for early dementia or other late life neurologic effects in this at-risk population**
 - **Provide a national source of ready and willing research volunteers for recruitment into TBI treatment studies**

CENC Study 1 Synopsis of Study Procedures



* Annual visit consists of select questionnaires & cognitive performance testing (Brief Test of Adult Cognition by Telephone (BTACT))

Study 1 Status; General Update Highlights

- Retention & f/u visits ongoing
 - Continued excellent visit completion rates
 - Maintaining integrity/quality of data and study conduct
- Successful transition of Data/Stats core
 - Released n=1,551 dataset
 - Released new user-friendly data dictionary and data request forms
- Scientific Analysis/dissemination ongoing, recent examples:
 - Some SM/V subgroups (young, Latino, PTSD, combat mTBI) have more missed study visits than others
 - Multivariable assessment (biomarker, imaging, and symptom) of SMs and Vs holds promise for developing finger-prints of lifetime exposure history of mTBI.
- Collaborations & Leveraging new funding ongoing, recent examples:
 - VA CSP Growth Hormone Stimulation in mTBI RCT
 - Amma Agyemang NIH Diversity Supplement grant; won award



CENC Lifetime Concussion diagnoses toolkit:

differences between internal and external versions

CENC Study 1

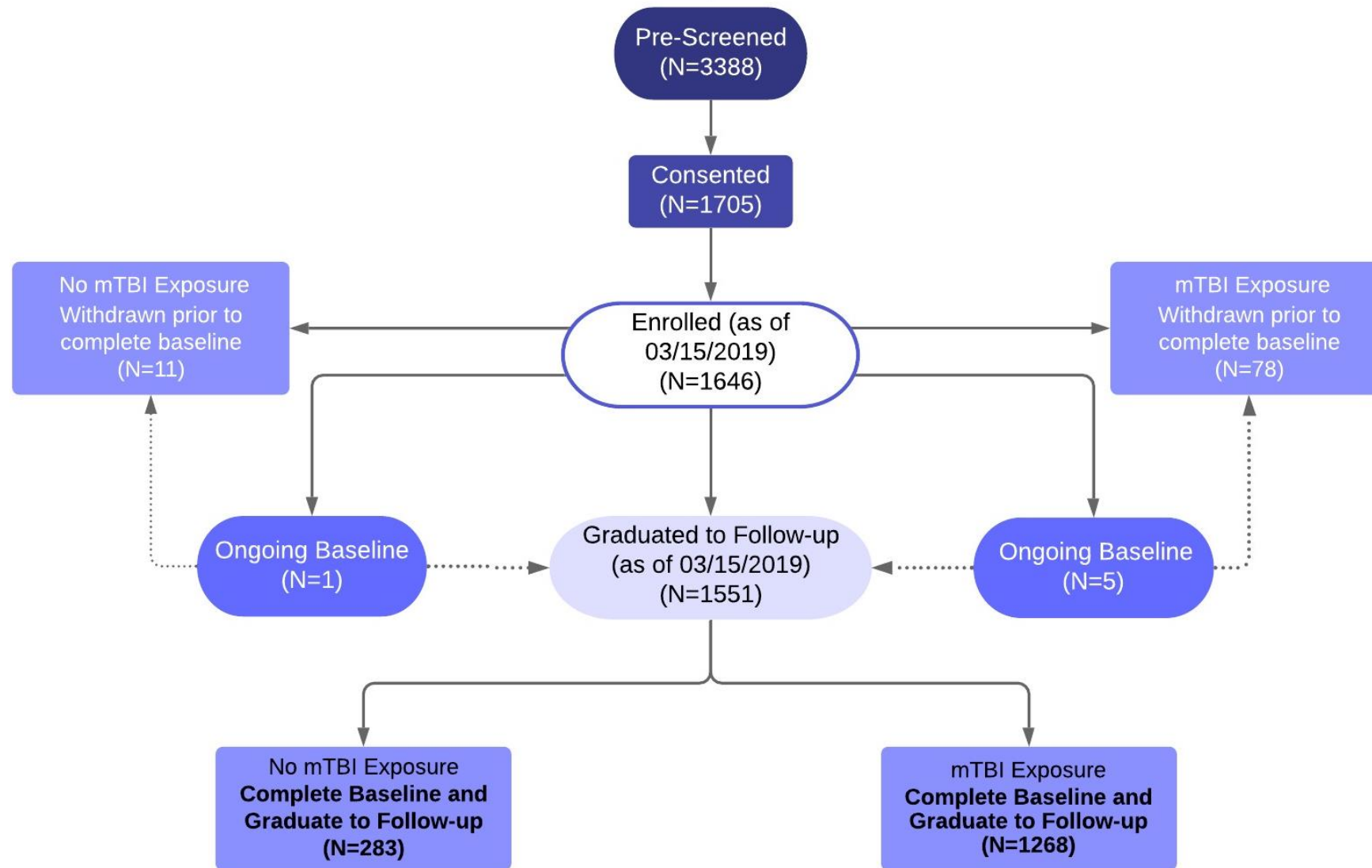
- Potential Concussive Event (PCE) mapping 2 parts, deployments and rest of life
- rCDI 2 versions, blast and general
- Automated preliminary mTBI diagnosis



External Version

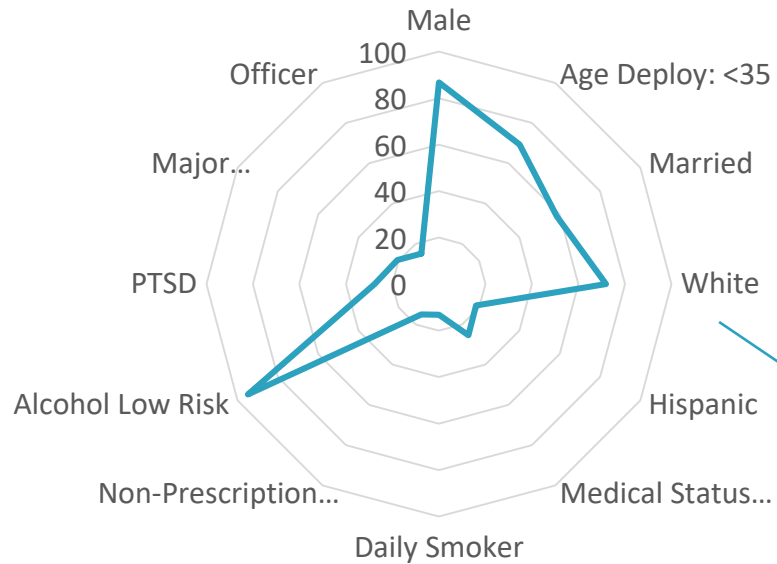
- PCE mapping 1 part combined
- rCDI single non-specific version, slightly abbreviated
- May be used to diagnosis all severity of TBI
- Provides algorithm for diagnostic guidance

Study Consort Diagram for Initial Evaluations



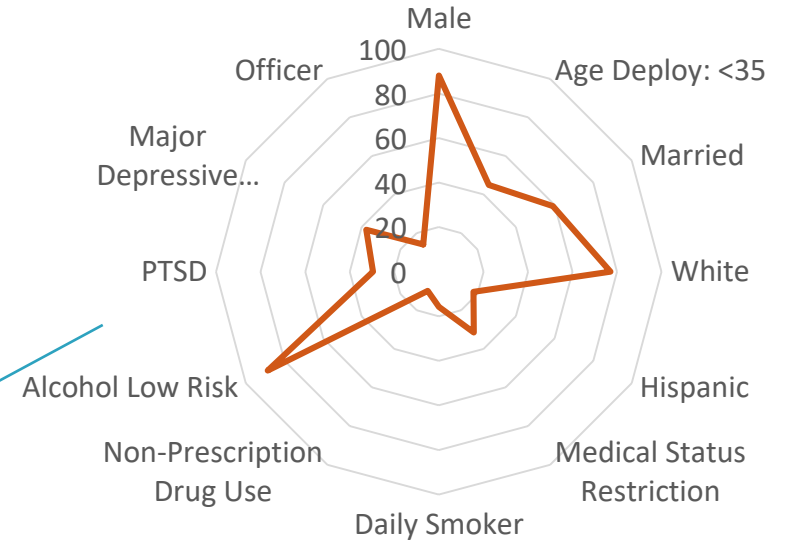
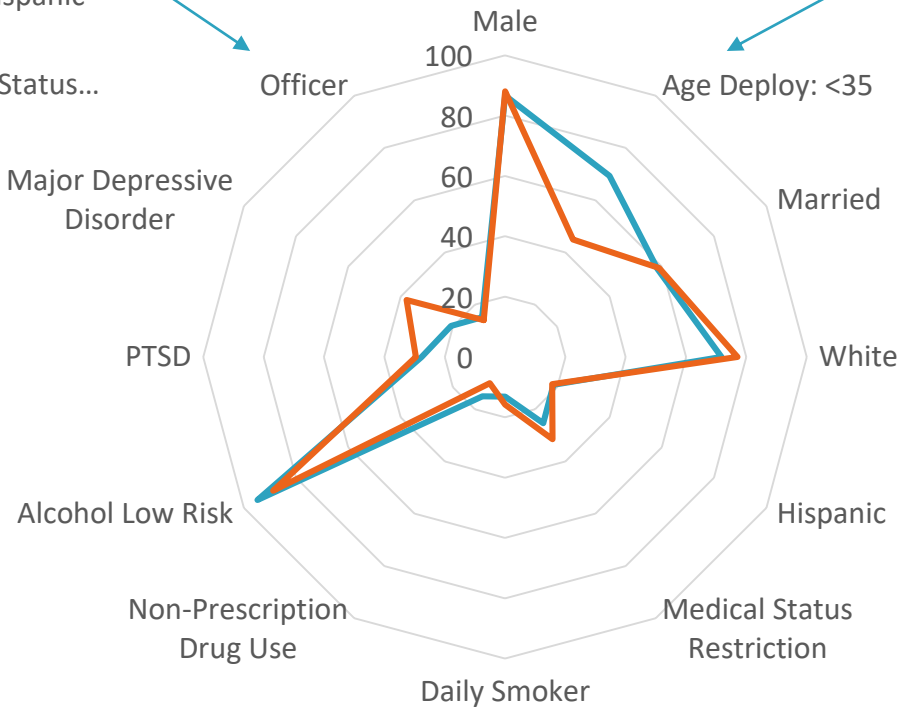
Comparison of Accrued Study Cohort to OEF/OIF Population

— CENC — General OEF/OIF/FO Population (average of all sources)



CENC Cohort

Comparing CENC to General OEF/OIF Cohorts



General OEF/OIF Cohort

Study Consort Diagram for Longitudinal Visits



Participant Level:

In-Person and Annual Phone visit completion counts combined across participants grouped by # of Past-Due Longitudinal Visits (LV)

(N= 453 Participants 1 LV due)

- Visit completed: 372
- Visit missed: 81

(N= 372 Participants 2 LVs due)

- Two visits completed: 230
- One visit completed: 96
- Both visits missed: 46

(N= 187 Participants 3 LVs due)

- Three completed visits: 105
- Two completed visits: 45
- One visit completed: 29
- All visits missed: 8

(N= 14 Participants 4 LVs due)

- Four completed visits: 8
- Three completed visits: 3
- Two completed visits: 2
- One completed visits: 1
- Missed Three Visits: 1

**Enrolled & Completed
Baseline (N=1,551)**

Withdrew from ongoing
Longitudinal visits (N= 100)
or Expired (N= 1)

**93.5% of the
Baseline Graduates
are still in the study**

Visit Level:

Longitudinal Visit completion rates
combined across type of visit

In-Person Follow-up: 446

- Completed: 361 (80.9%)
- Missed: 85 (19.1%)

Annual Phone Assess: 1368

- Completed: 1,047 (76.5%)
- Missed: 321 (23.5%)

CENC BIOREPOSITORY CORE

Kimbra Kenney, M.D.

Jessica Gill, R.N. PhD.

Brian Cox, Ph.D.



Biorepository – Curate, Store and Available for Analysis

- Established Biorepository at USUHS Twinbrook Site: as of 15 JUN 2019, over 48 months (1st submission in 6-2015), received 172 shipments of ~ 10 locally processed, de-identified specimens each from:
 - 1,719 Study 1- multisite longitudinal study, PI W Walker, Richmond VA (1,462 baseline & 257 paired serial follow-up specimen collections) participants
 - 144 Study 49 (PI Nick Davenport, Minneapolis VA) participants
 - 20 Study 20 (PI Amy Jak, San Diego VA) study participants
- with >27,000 aliquots of extracted DNA, plasma, serum, saliva, and RNA (PaxGene) available for analysis to CENC and CENC-affiliated study teams after CENC specimen/data request approval by CENC Research Committee (Chair, Laura Manning PhD, VCU, Richmond VA).
- Completed: neuroendocrine screen (TSH, IGF-1, testosterone) on 1,431 CENC Study 1 subjects at CLIA-certified lab (Quest).
- Completed: DNA extraction & APOE genotyping on 1,281 Study 1 & 49 participants with consent for DNA extraction and genetic testing. Remaining with consent in process and analysis underway of APOE and chronic neuro outcomes.
- Extracted DNA from 1,281 for GWAS testing pending project funding and minimum 2,000 available for analysis in collaboration with other TBI GWAS studies (e.g. Center-TBI, TRACK-TBI, Million Vet Project).

Biomarker Discovery Project- Background

Few studies of TBI biomarkers in the *chronic* stage or of *remote* (≥ 2 years) TBI effects, majority focus on acute/subacute TBI:

- **Olivera et al, JAMA Neurology, 2015 (SIMOA):** 70 AD mTBI (MAMC), 16 mo post-deployment, \uparrow plasma tau in repetitive TBI and \uparrow tau correlated with NSI
- **Stern et al, J AD, 2016:** 78 Retired NFL, \uparrow exosomal tau and \uparrow correlated with PSI & verbal memory, but not depression or symptoms
- **Rubinstein et al, JAMA Neurology 2017 (SOFIA):** \uparrow plasma p-tau/t-tau ratio in 21 TBI (1-8 mos) compared to HC
- **Gill et al, Brain Injury, 2018 (SIMOA):** 42 AD mTBI (MAMC), \uparrow CNS-derived exosomal tau/A β 42/IL-10 and exo tau correlated with NSI
- **Yaffe, Kenney, Gill, AAIC, 2018, under review (SIMOA):** 122 aged NH veterans (mean age 78) with remote TBI (>30 yrs), found \uparrow IL6, \uparrow NFL, \uparrow GFAP, and \uparrow pTAU in neuronally-derived exosomes in TBI c cognitive impairment (CI), N = 35, compared to TBI without CI, N = 30 and non-TBI age-matched controls, N = 57

Even fewer studies of miRNA expression studies in TBI, majority small in number, NONE to date in the *chronic* stage:

- **Di Pietro et al, J Neurotrauma, 6-2017:** miRNA from 5 mTBI, 5 sTBI, & 5 HC at 1 and 15 days p injury. 2 miRNA in mTBI up and 2 down regulated. miR-425-5P prognostic @ 6 mos
- **Hicks et al, J Neurotrauma, 1-2018:** Salivary miRNA from 60 ped mTBI (0-14 days after mTBI) and 18 HC; 4 down regulated and 2 upregulated in mTBI compared to HC
- **Di Pietro et al, Front Mol Sci, 8-2018:** In 10 acute concussed pro rugby and 10 non-concussed, found 5 salivary miRNA collected 2-3 days after injury significantly upregulated in concussed athletes and correlated with reaction time performance
- **Papa et al, J Neurotrauma, 10-2018:** 23 football athletes and 30 controls; Athletes with declining cognitive function over football season, had increased expression of 6 miRNA
- **LaRocca et al, PLOS1, 1-2019:** 50 amateur MMA fighters with 216 samples at 0-21 days p bout. 21 with significant expression change post-fight and 4 down-regulated in mTBI.

Biomarker Discovery Project- Background

PROPOSED: CENC cohort TBI Outcomes Biomarker Discovery Project

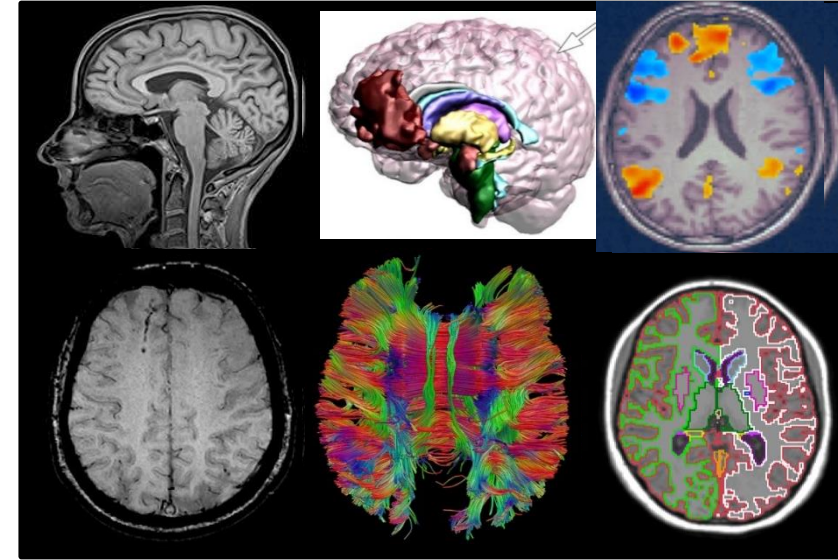
Interim analysis of 200 well-characterized CENC Longitudinal Study subjects from CENC data snapshot (100 mTBI with LOC/PTA, 50 mTBI with AOC only, 50 TBI negative), as follows:

1) Exosomal and plasma protein biomarker analysis, using Quanterix SIMOA ultrasensitive assays from plasma and peripherally circulating exosomes and correlation with clinical outcomes (NSI, PCL-5, PHQ-9) neurocognitive assessments, APOE genotype and advanced neuroimaging of following 9 candidate chronic TBI biomarkers:

- Neurodegeneration ($A\beta 40/A\beta 42$, total tau/p-tau, NFL)
- Neuroinflammatory (IL-6, IL-10, TNF- α)
- Vascular (VEGF)

2) miRNA expression analysis of peripherally circulating exosomes (plasma and saliva) and correlation with chronic TBI symptoms and outcomes

IMAGING CORE



Dr. Elisabeth Wilde

Ready for Implementation

- Monitoring of WMHs for increase in size/number or dynamic change
- Reduction of distortion in diffusion data
- Enhanced QA efforts
 - Increased automation in QA metrics
 - Use of novel phantoms

Areas Requiring Additional Scientific Inquiry

- Harmonization of data
- Longitudinal data analysis
- Further examination of spatial distribution, phenotypes and subgroups
- Multimodal analysis
- Novel pipeline development
- Further comparative testing
- Individualized analysis to be used in treatment evaluation

Contribution to Larger Consortia Efforts

- Enhancing NeuroImaging and Genetics Meta-AnalysIs (ENIGMA)
 - TBI-based efforts are led by Drs. Wilde, Tate, and Dennis
 - Military, ED-based, pediatric, sports-related concussion, and IPV/non-accidental
 - Mega- and meta-analyses, with participation from (military subgroup)

• CENC	NICoE	TRACTS
• CARE	iSCORE	BIMA
• ENIGMA PTSD	ADNI-DoD	InTRUST
• Individual Merit Reviews		
 - Ongoing analyses examining diffusion and volumetric measures
 - Data harmonization efforts and meta-analysis for data already collected
 - Recommendations for prospective harmonization and CDEs
 - Novel pipelines to address automated WMH analysis

CENC STUDY 4: EPIDEMIOLOGY OF MTBI AND NEUROSENSORY OUTCOMES

Mary Jo Pugh, Ph.D.



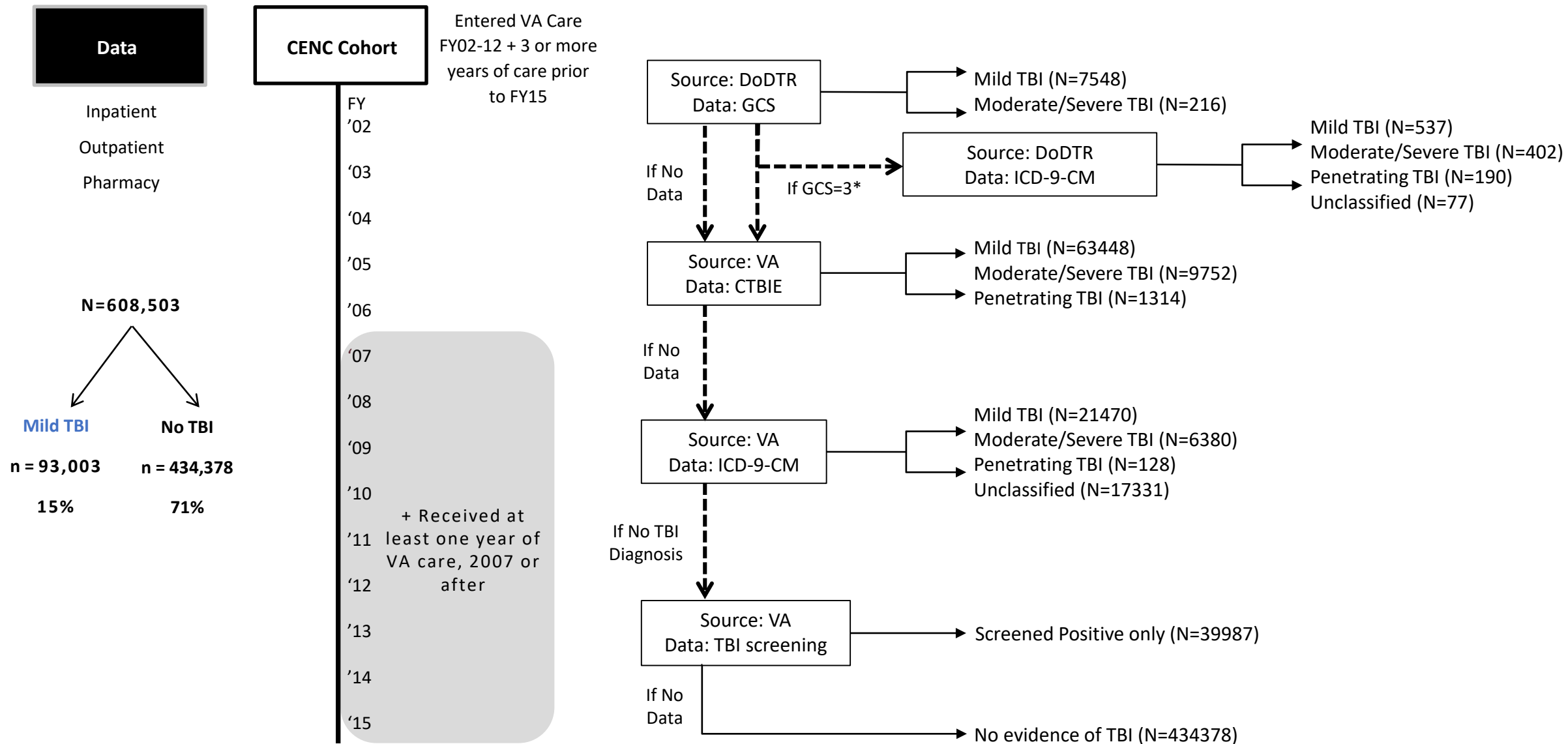
Overall Goals

To identify long-term outcomes of mTBI in comparison to no TBI and more severe TBI

Aims

1. Examine the association of TBI severity with neurosensory and other neurodegenerative outcomes in deployed Post-9/11 Veterans
2. Identify trajectories of comorbidity in deployed Post-9/11 Veterans with mTBI vs. no TBI

Cohort of Post-9/11 Veterans in VA Care



Measures

Comorbidity Conditions

Identified Using ICD-9 codes

Mental Health

PTSD, Substance Use Disorder (SUD),
depression, anxiety

Possible TBI Sequelae

Tinnitus, hearing loss, vestibular, blurry
vision, blind, cognitive, pituitary, seizure,
cerebrovascular

Pain

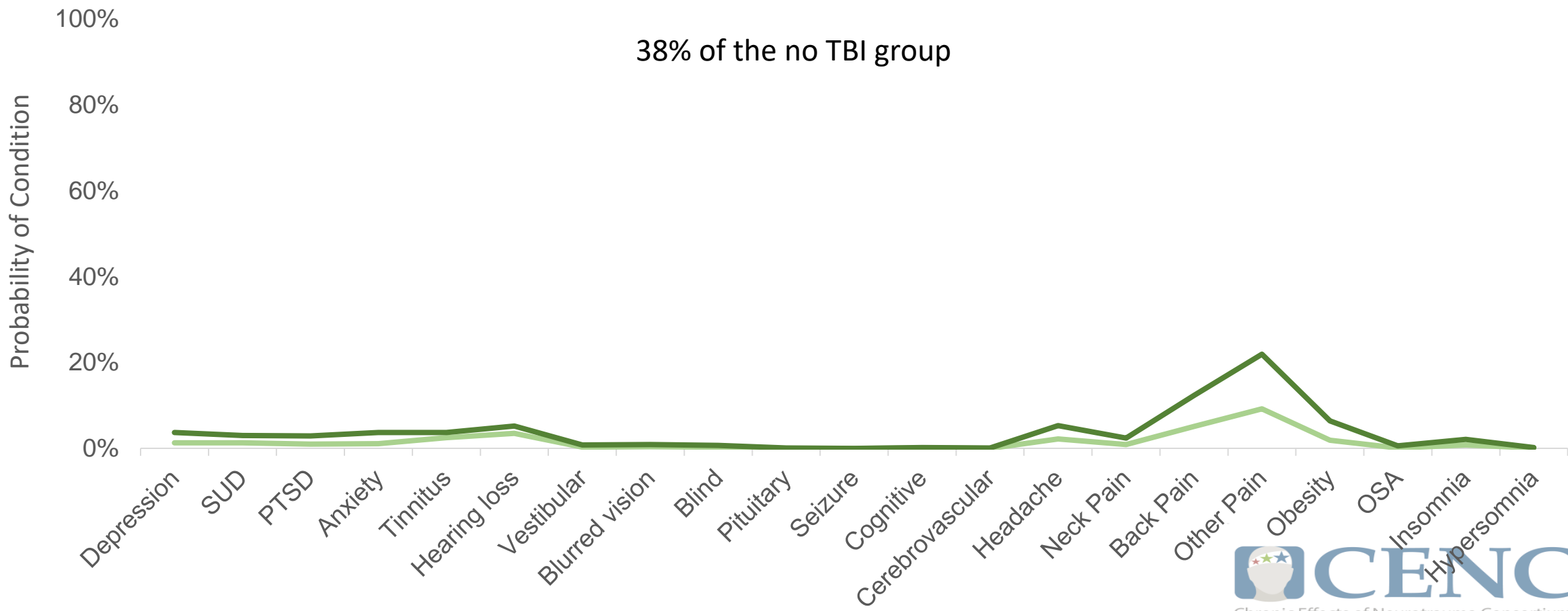
Headache, neck pain, back pain, other pain

Weight & Sleep

Obesity, obstructive sleep apnea (OSA),
insomnia, hypersomnia

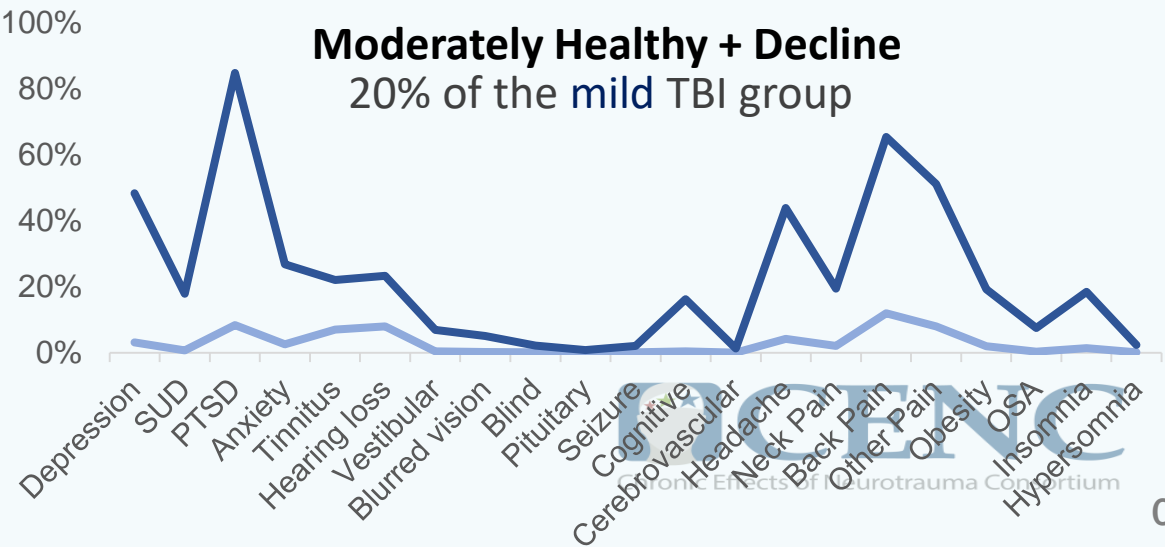
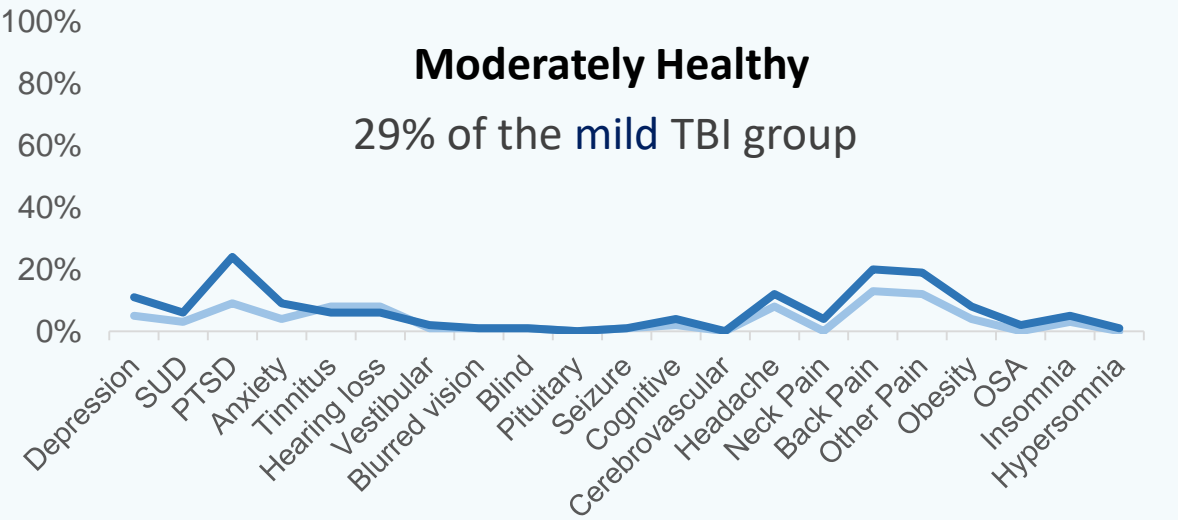
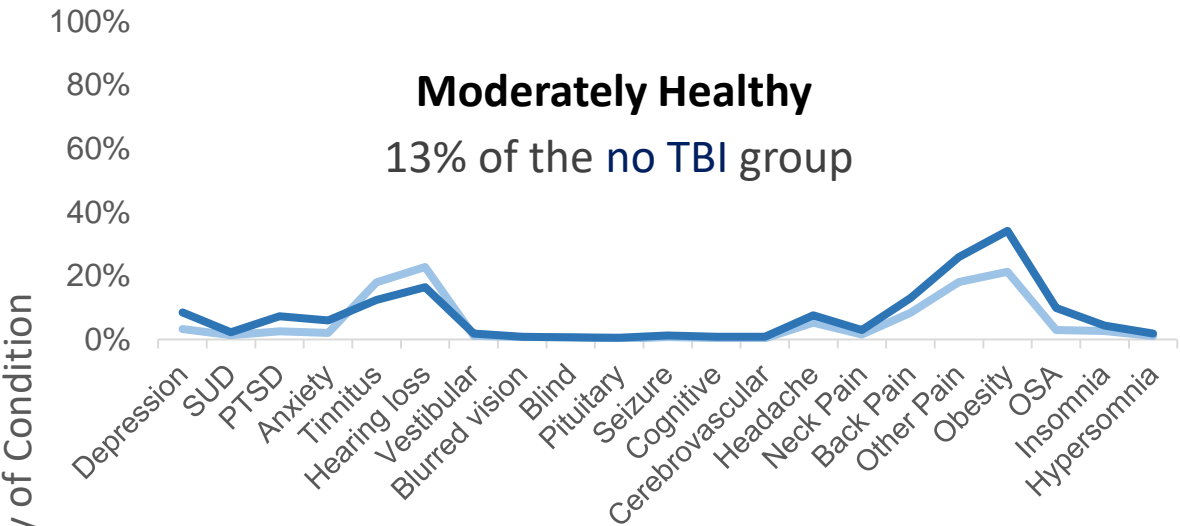
Healthy

Year 1 v. Year 5



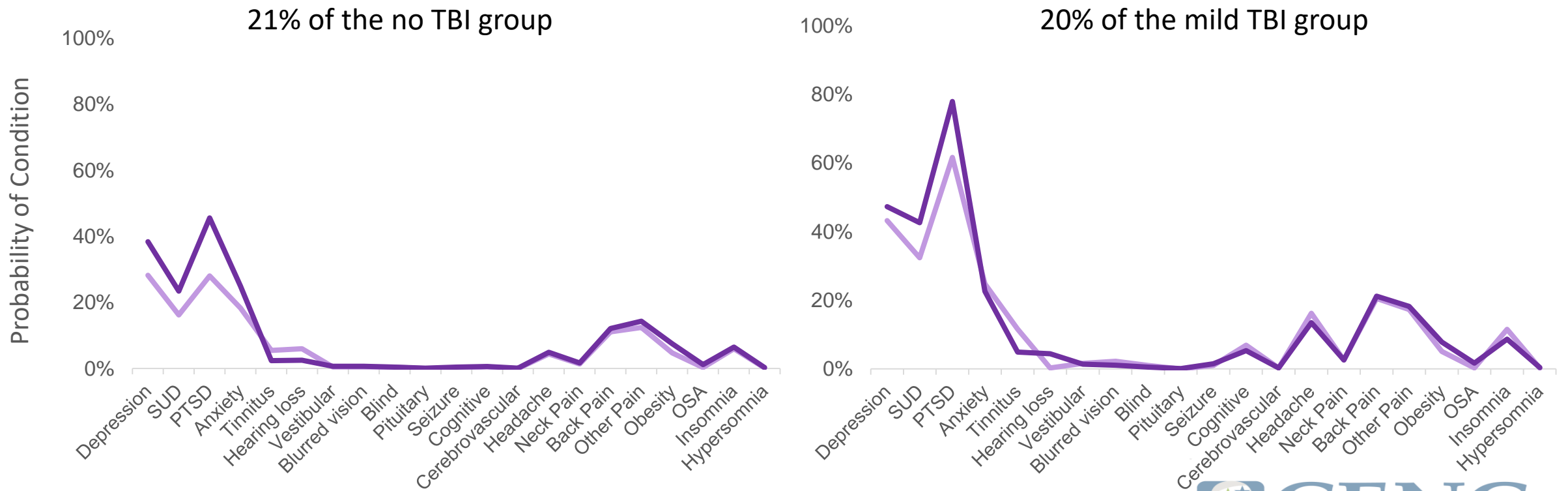
Moderately Healthy

Year 1 v. Year 5



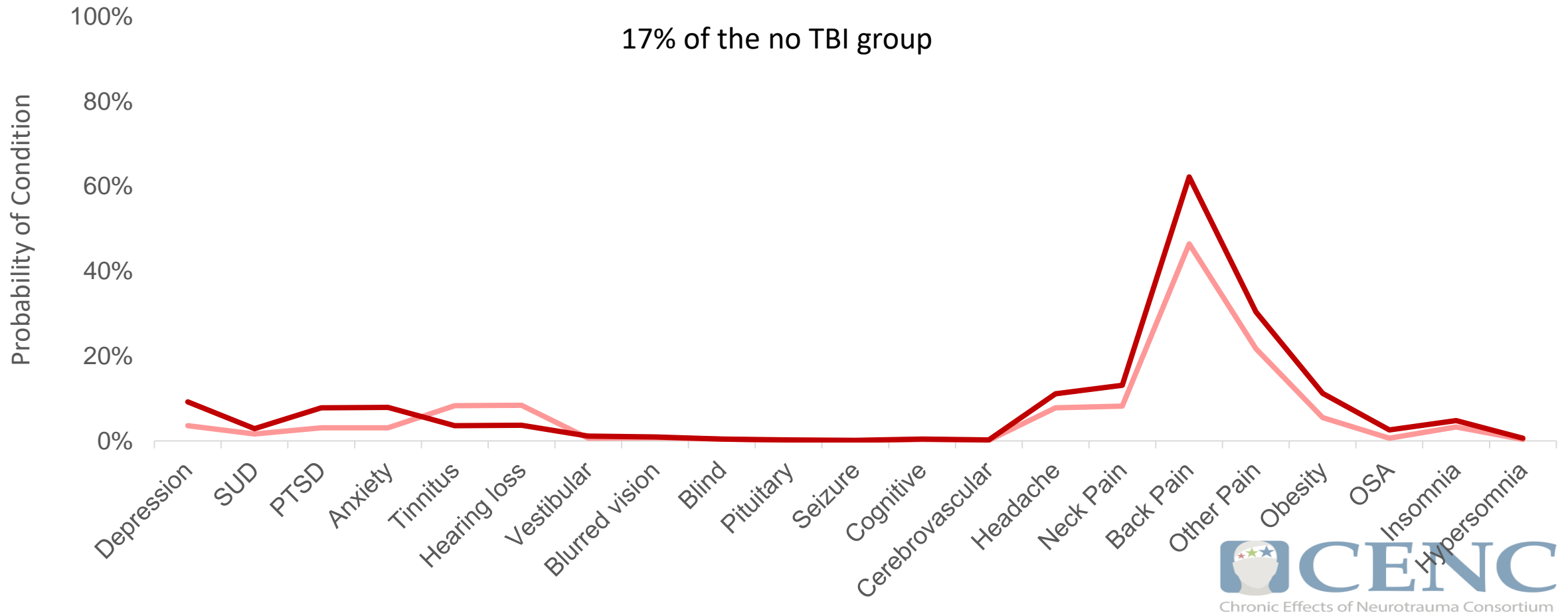
Mental Health+SUD

Year 1 v. Year 5



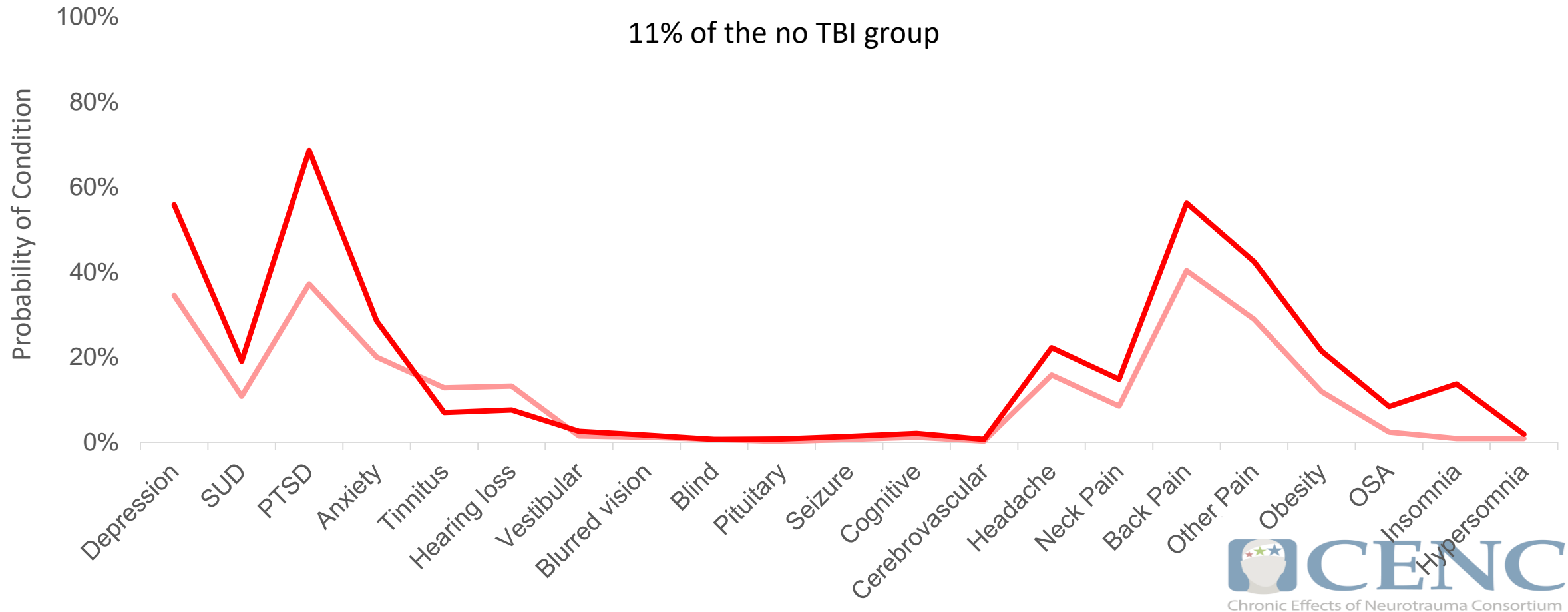
Pain

Year 1 v. Year 5



Mental Health LOW SUD + Pain

Year 1 v. Year 5



Adverse Outcomes in Mild TBI Phenotypes

Comparator: Moderately Healthy

3

Adjusted Odds Ratio

2

1

0

Overdose

Suicide-Related Behavior

Mortality

Start healthy to worse

MH with High SUD

PCT

PCT to better

Start healthy to worse

MH with High SUD

PCT

PCT to better

Start healthy to worse

MH with High SUD

PCT

PCT to better

1.29

2.00

1.24

0.57

1.45

1.86

1.49

0.65

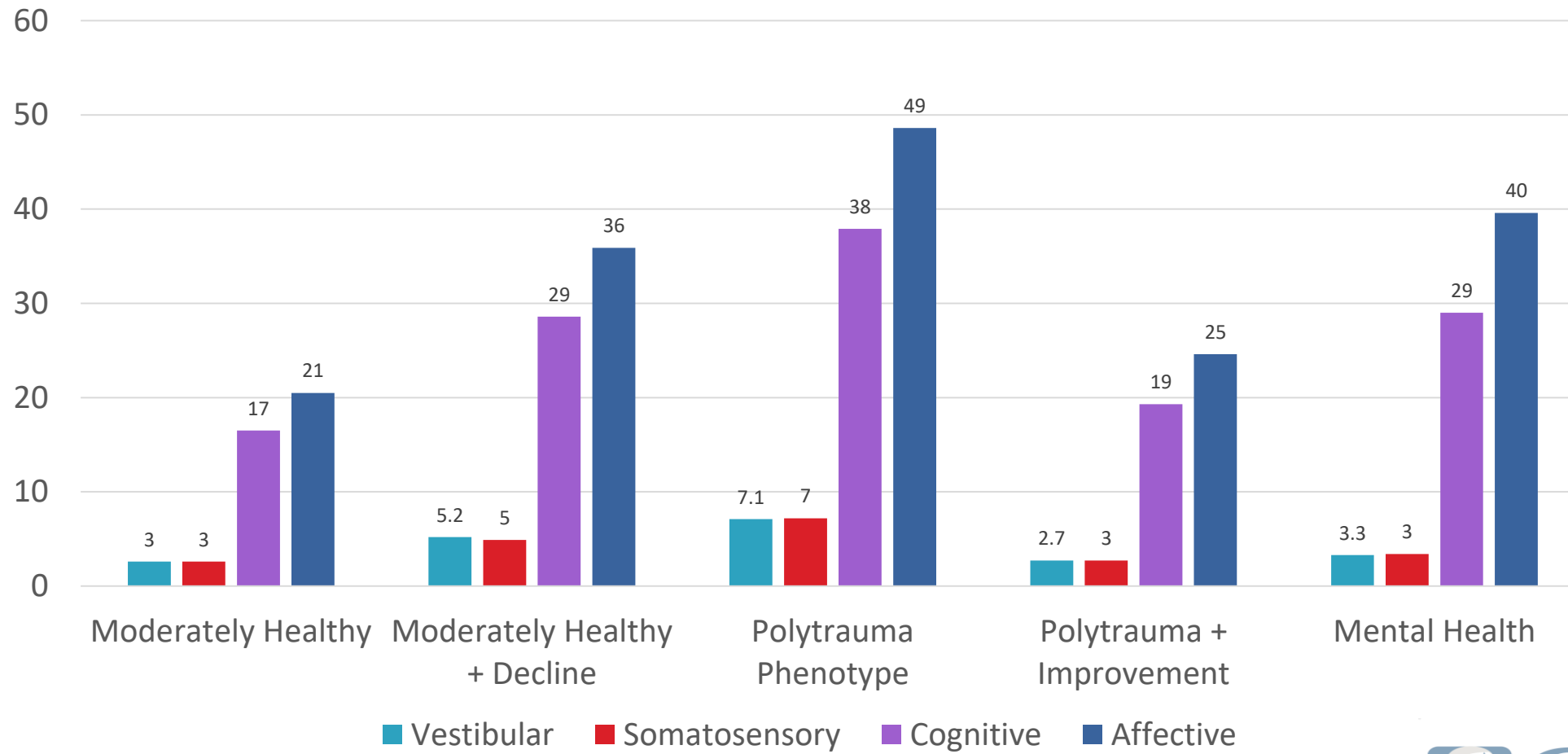
1.42

1.49

1.31

0.85

Neurobehavioral Symptoms by mTBI Phenotypes



Differences Between Key Comorbidity Phenotypes

Moderately Healthy + Deteriorate vs.
Sort of Healthy

Deterioration phenotype

- **Less likely to have**

- Guard/Reserve service
- Multiple deployments

- **More likely to have**

- DoD TBI diagnosis
- DoD Mental Health diagnosis
- Homelessness/Suicidal Ideation or Attempt/Overdose early in VA care
- 5 or more CNS active medications/year

Polytrauma vs.
Polytrauma+Improvement

Improvement phenotype

- **Less likely to have**

- DoD TBI diagnosis
- DoD Mental Health diagnosis
- 5 or more CNS active medications/year
- Homelessness/Suicidal Ideation or Attempt/Overdose early in VA care

- **More likely to have**

- Multiple deployments

What Does It Mean?

- mTBI has significant impact on all neurosensory conditions
- Impact for auditory and multisensory dysfunction exacerbated by blast
- TBI not associated with ALS
- There are distinct phenotypes, with divergence over time, that are predictive of adverse outcomes that are important to Veterans, VA and society

What Next?

- Quality of Care studies
- Identify DoD TBI phenotypes
 - use DoD health system/Theatre data with structured data and natural language processing (incorporate mechanism of injury)
- Use deep learning approaches to
 - Identify feature importance of TBI phenotype in emergence of neurodegenerative disease, substance use disorder (SUD), neurosensory dysfunction, chronic pain, mental health
- Use reinforcement learning models
 - that incorporate TBI phenotypes and ***acute/chronic treatment approaches*** to develop dynamic risk scores for neurosensory dysfunction, neurodegenerative disease, SUD, self-harm behaviors, poor military outcomes

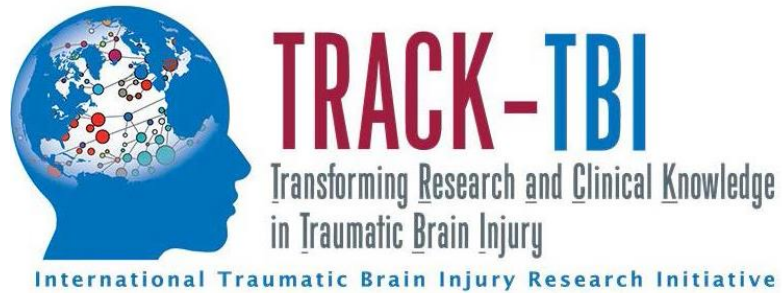
MTBI EXPOSURE MECHANISM AND SERVICE-CONNECTED DISABILITY, VHA DIAGNOSES, UTILIZATION AND COST

Clara E. “Libby” Dismuke-Greer, PhD





**15 Year
Longitudinal
Studies**



A collaborative for advancing diagnosis and treatment of TBI



Thank you to the entire CENC/LIMBIC Team:

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<https://www.cencstudy.org/>



Thank You !

<https://www.cencstudy.org/>