32nd Annual Brain Injury Alliance of Colorado Conference

A Medical and Legal Perspective on the Standard of Care

November 6, 2015

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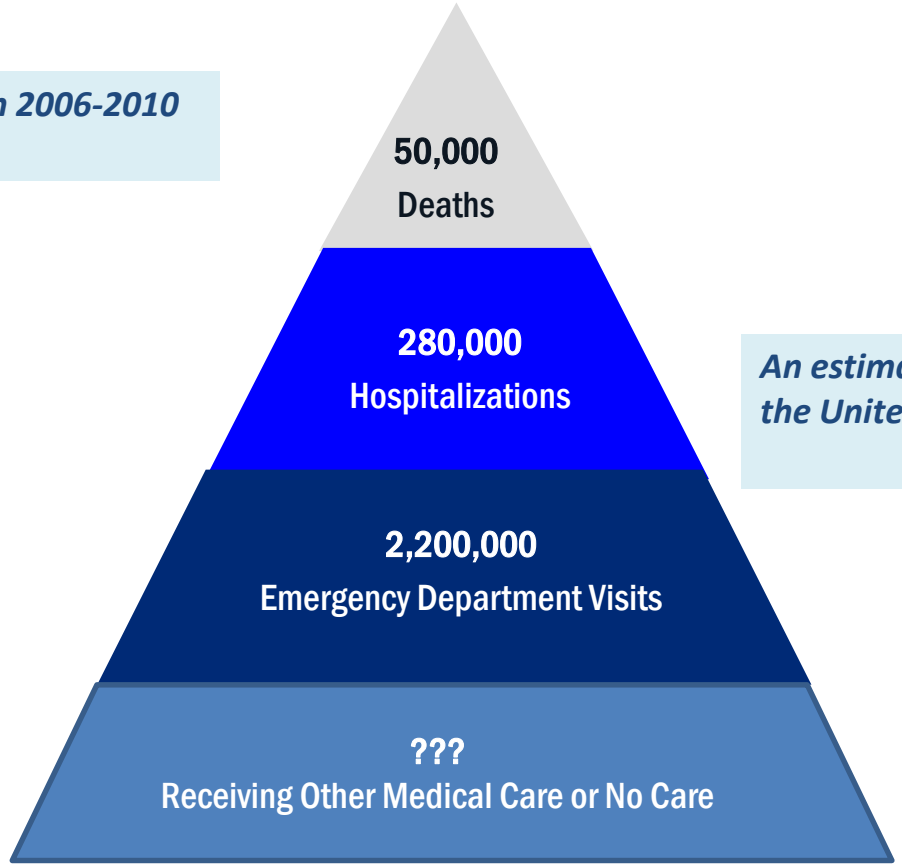
Estimated Average Annual Number of TBI in the United States

CDC estimates from 2006-2010 data:



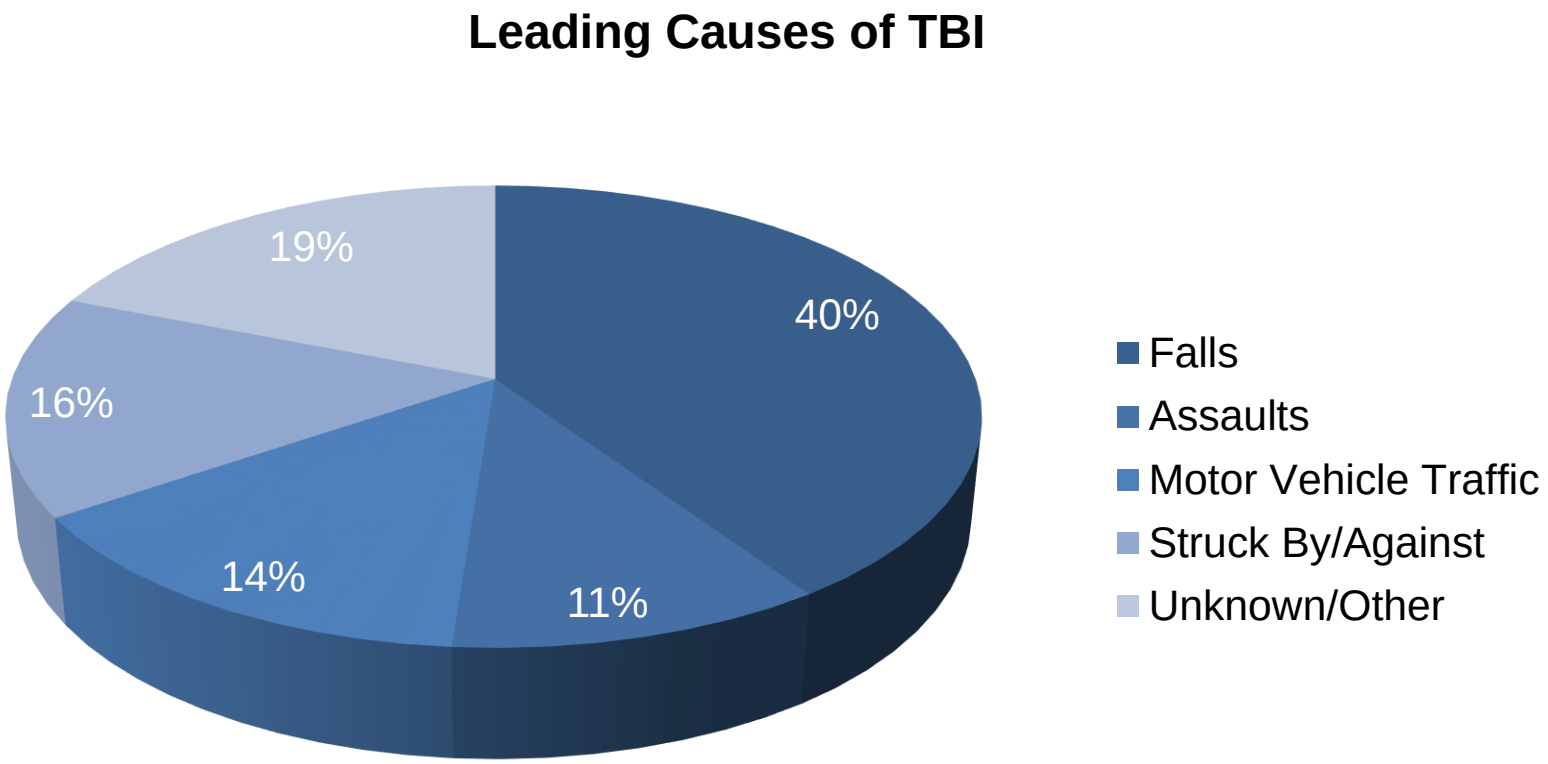
An estimated 2.5 million TBIs occur in the United States annually.

In 2009, approximately 3.5 million patients were treated with a TBI listed as primary or secondary diagnosis.

Sources: Centers for Disease Control, 2014. http://www.cdc.gov/traumaticbraininjury/get_the_facts.html

Coronado, V, McGuire, LC, Sarmento, K, Bell, J, Lionbarger, MR, Jones, CD, Geller, AI, Khoury, N, Xu, L. (2012). Trends in Traumatic Brain Injury in the U.S. and the public health response: 1995-2009. *Journal of Safety Research,*. 43(4), 299-307.

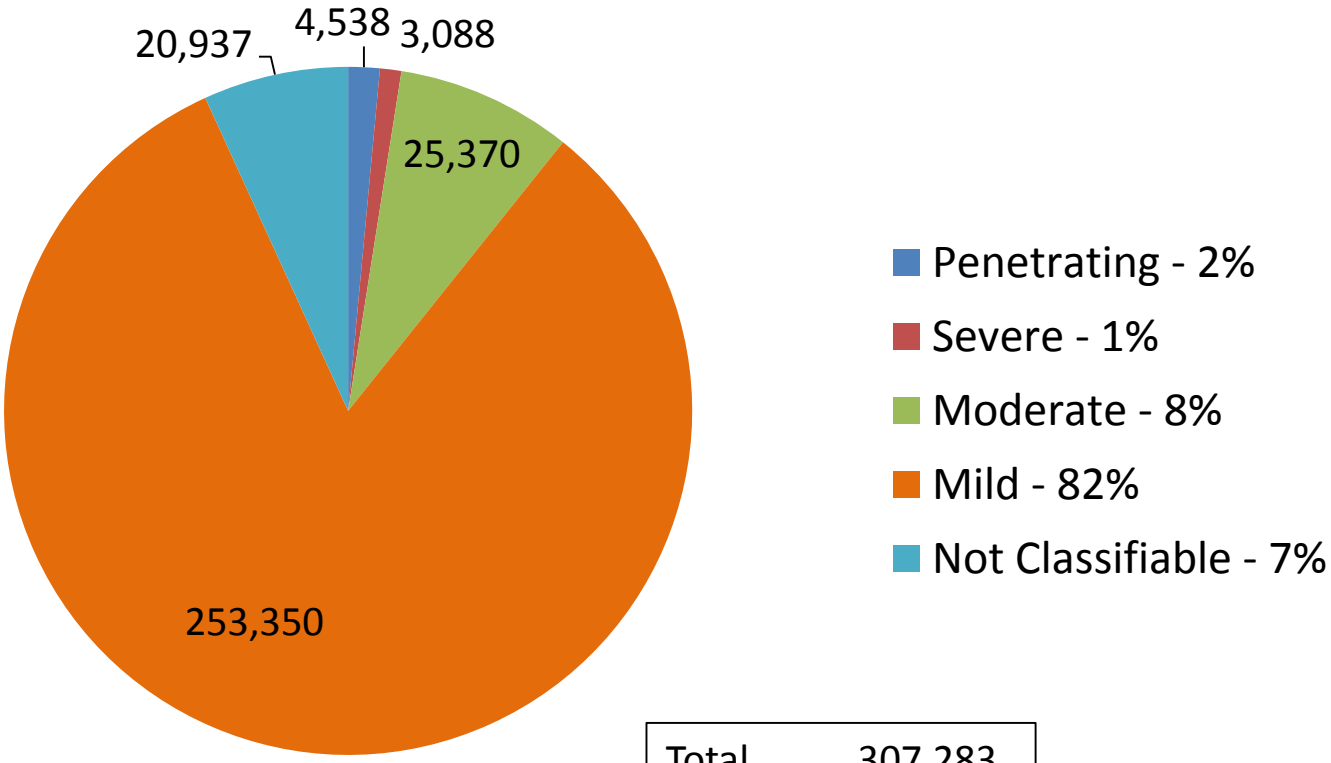
Estimated Average Percentage of Annual TBI by External Cause in the United States 2006-2010



Source: Centers for Disease Control, 2014. http://www.cdc.gov/traumaticbraininjury/get_the_facts.html

TBI Numbers By Severity

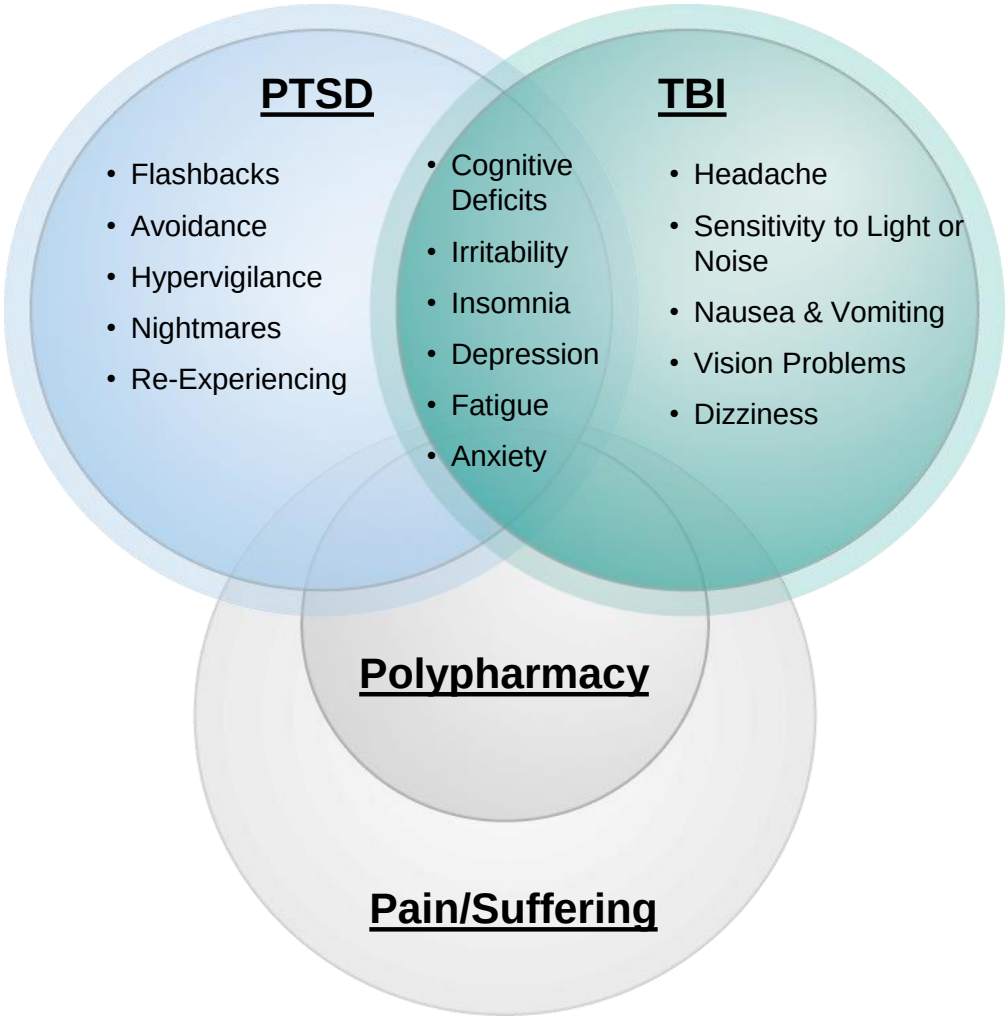
DoD Numbers for Traumatic Brain Injury
'00 – '14 Q2 Totals



Total	307,283

Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Center (AFHSC)

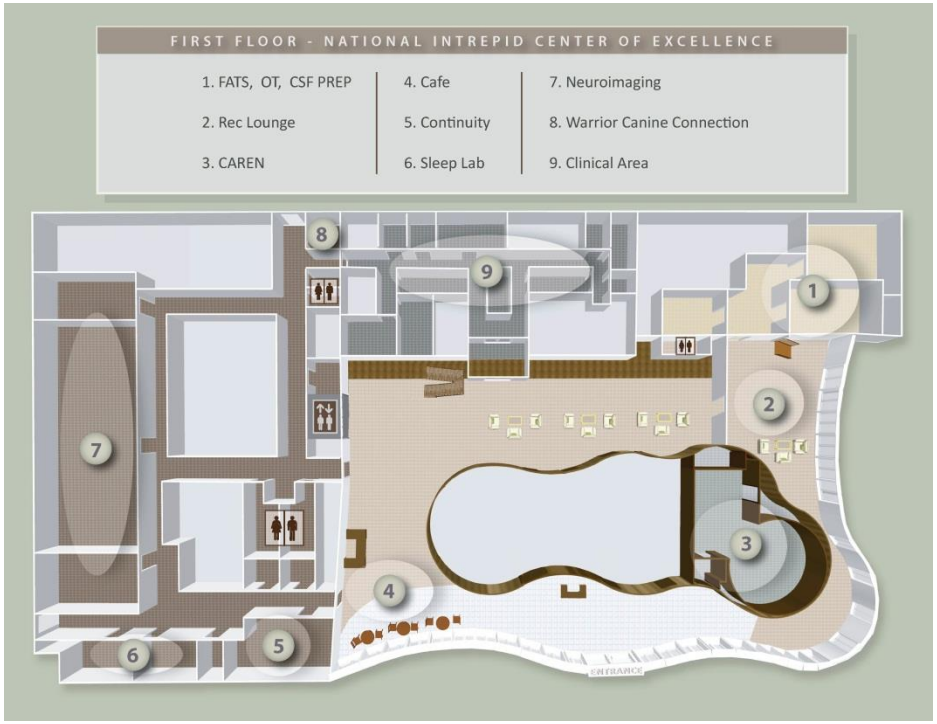
Medical Imperative: Challenging Co-morbidity

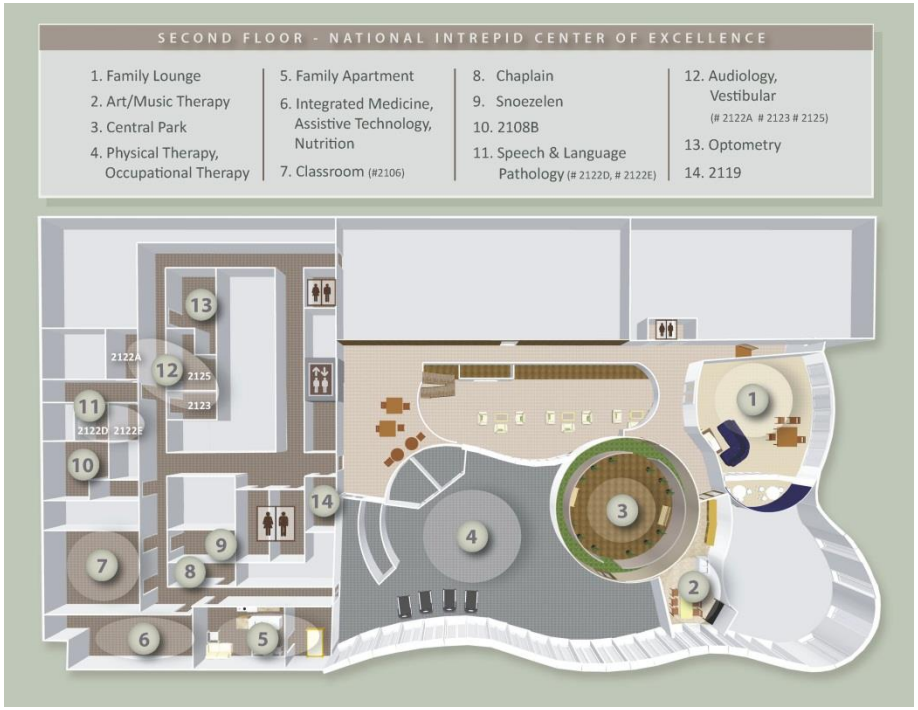


THE NATIONAL INTREPID CENTER OF EXCELLENCE

an instrument of hope, healing, discovery and learning

NICoE Floor Plan






STRIDE
QUANTUM

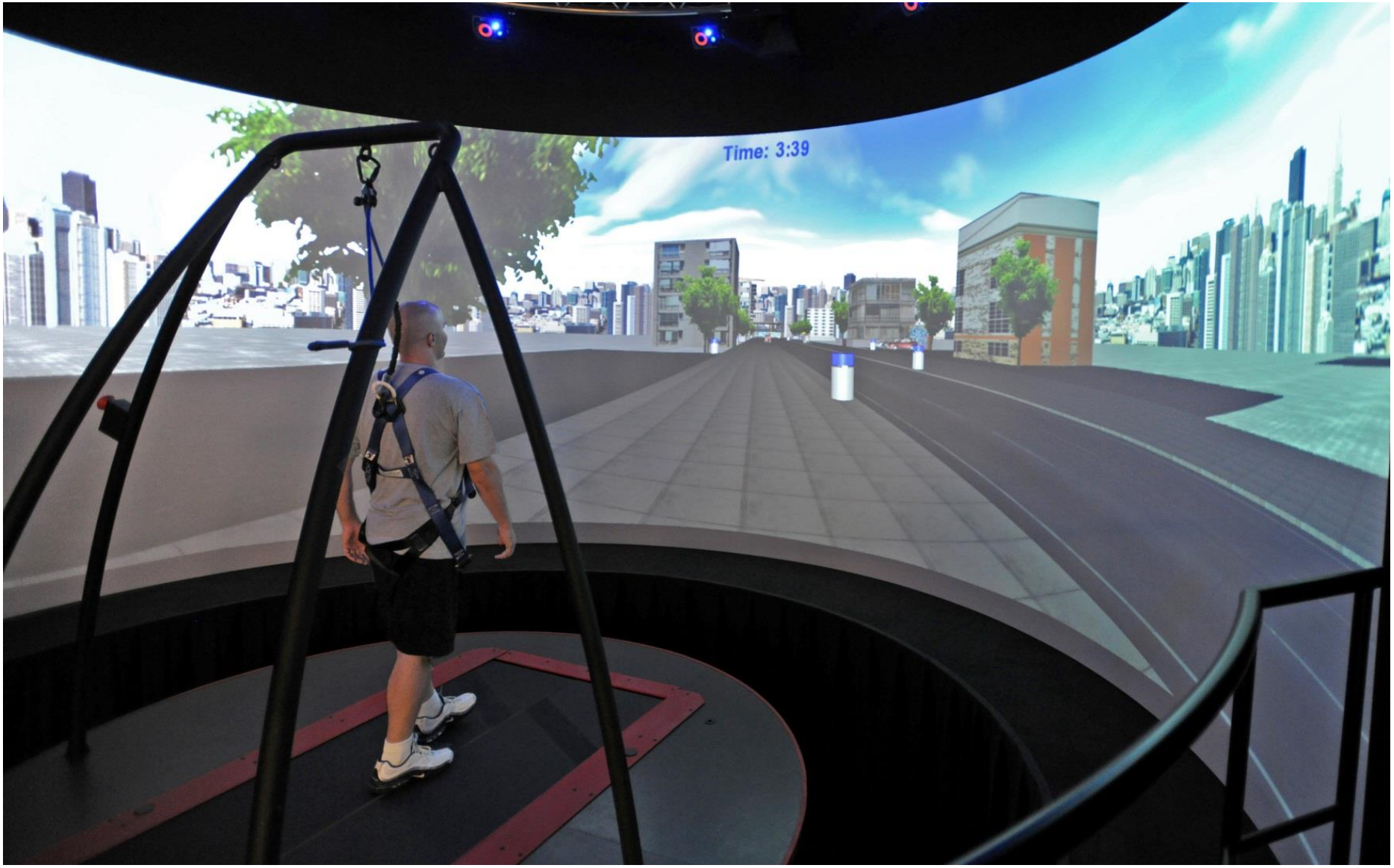
Passageway

Central Park

Warriors Lounge

Family Lounge

Apartment



CAREN

Server Room

NICoE Overview

Vision: To be the nation's institute for traumatic brain injury and psychological health dedicated to advancing science, enhancing understanding, maximizing health and relieving suffering.

Mission: The National Intrepid Center of Excellence is dedicated to advancing our understanding of traumatic brain injury (TBI) and psychological health (PH) conditions. We diagnose and initiate treatment for patients referred with complex, comorbid TBI/PH conditions; conduct focused research, and export knowledge and practices to improve TBI and PH outcomes for service members, their families and the Military Health System (MHS).

- **Clinical**: A model of holistic, interdisciplinary evaluation and treatment in a family focused, collaborative environment that promotes physical, psychological and spiritual healing of service members (SM) with the complex interaction of TBI and PH conditions

- **Research**: A DoD Institute with a unique patient base and the most current technical and clinical resources for initiating innovative pilot studies designed to advance the characterization of the pathophysiology of the comorbid state, while additionally serving as a "hub" for exchanging information among partners in federal, academic and satellite locations

- **Training and Education**: An educational platform that serves as the nexus for sharing of information, best practices and creation of new concepts. NICoE SMEs influence improvements in care through knowledge translation via scientific publications and national and international academic speaking engagements.

NICoE has seen **700** cohort Patients through August 2014

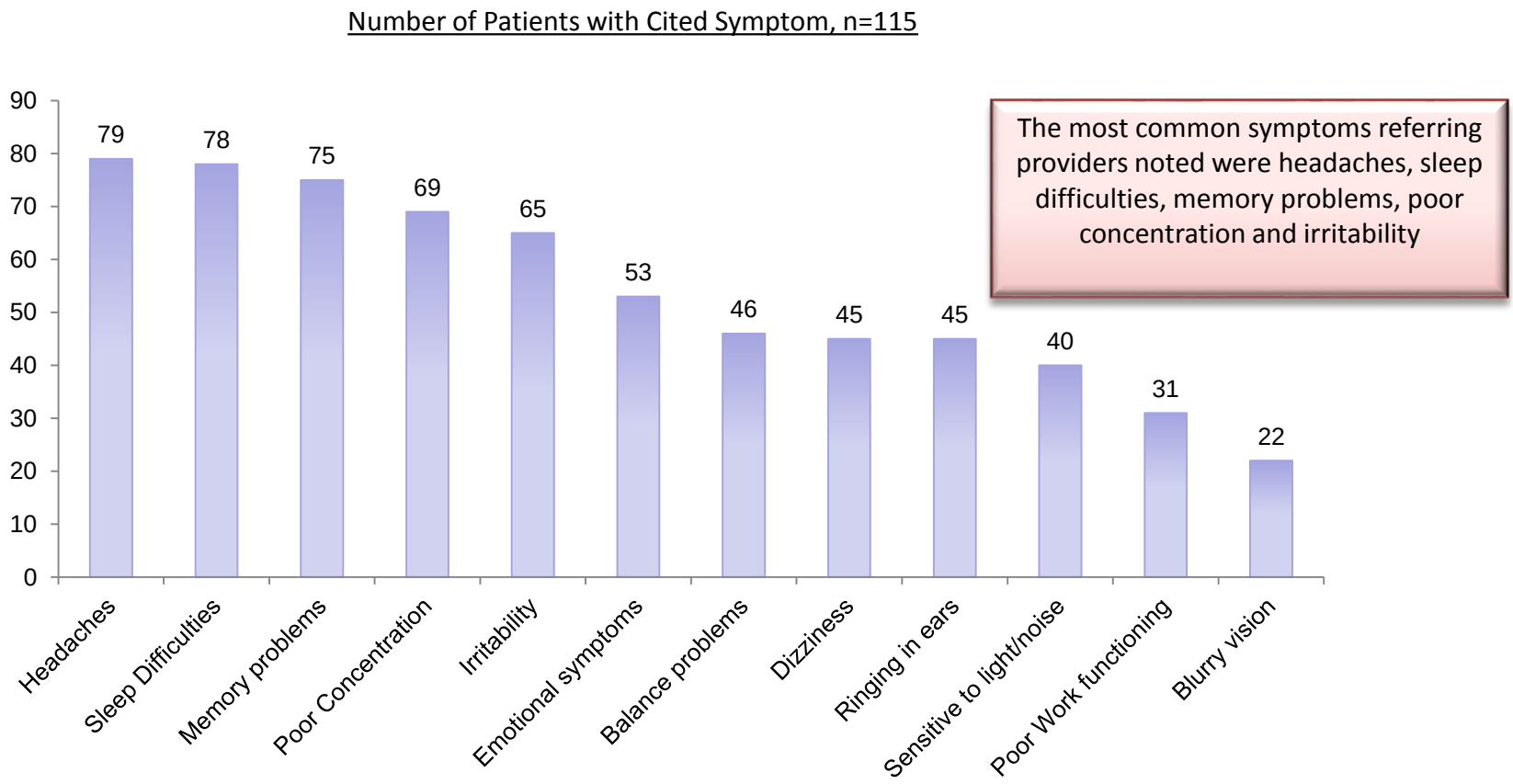
Breakdown of Patients Admitted by Service, October 2010 – August 2014

	161 Marine	252 Army	230 Navy	56 Air Force	1 Coast Guard
Referral Sources by Service	Camp Lejeune, NC Quantico, VA WRNMMC Bethesda, MD NNMC Bethesda, MD Camp Pendleton, CA SOCOM Cherry Point, NC Fort Belvoir, VA Parris Island, SC Indianhead, MD	CBWTU-AR SOCOM Fort Hood, TX Fort Campbell, KY Fort Huachuca, AZ Fort Riley, KS WRAMC, DC Fort Meade, MD Fort Drum, NY Fort Bliss, TX	SOCOM NNMC Bethesda, MD Patuxent River, MD Camp Lejeune, NC Virginia Beach, VA WRNMMC Bethesda, MD Fort Belvoir, VA Naples, Italy Quantico, VA Naval Branch Health Clinic Groton, CT	SOCOM Eglin AFB, FL Dover AFB, DE Peterson AFB, CO Pope Field, NC Tyndall AFB, FL WRNMMC Bethesda, MD Newport, RI Fairchild AFB, WA WRAMC, DC	USCG Traverse City

The chart above reflects the top 10 referring installations by service.

Source of Data: NICoE Referral Forms, Admission Calendar, and AHLTA, Continuity Management Access Database

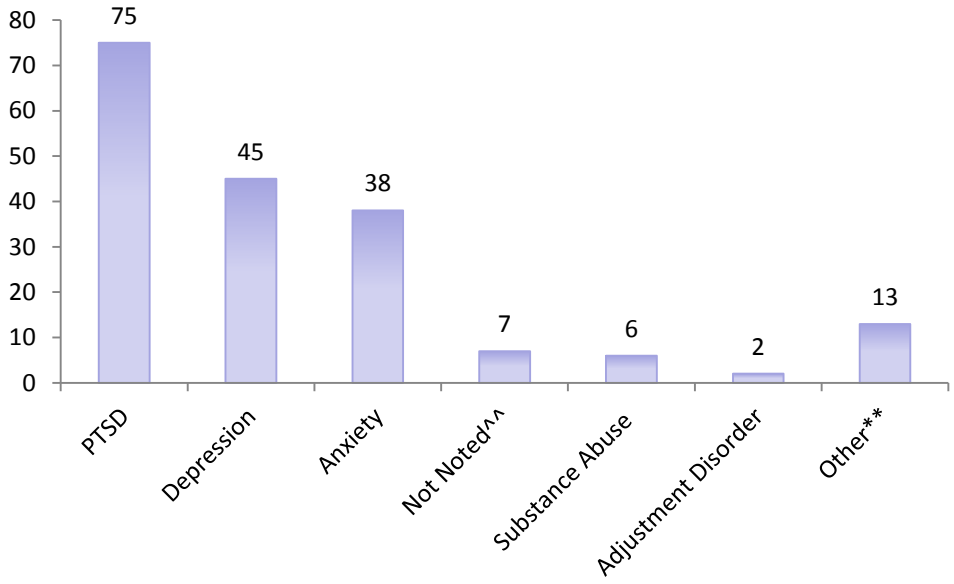
NICoE Patients
Symptoms Cited
At Time of Referral



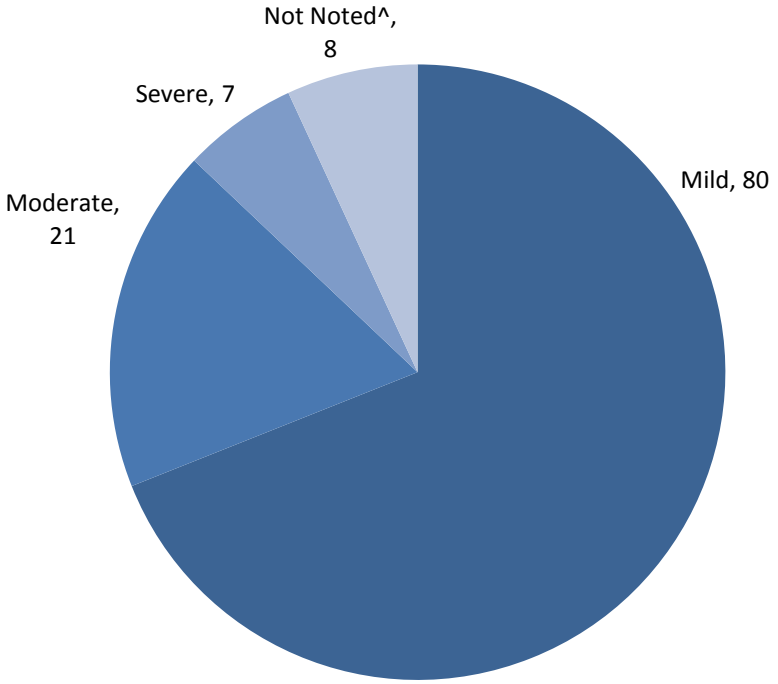
Source of Data: NICoE Referral Forms

NICoE Patients
Psychiatric Diagnoses and TBI Severity as Determined By Referring Provider

Patients by Psychiatric Diagnosis, n=115*

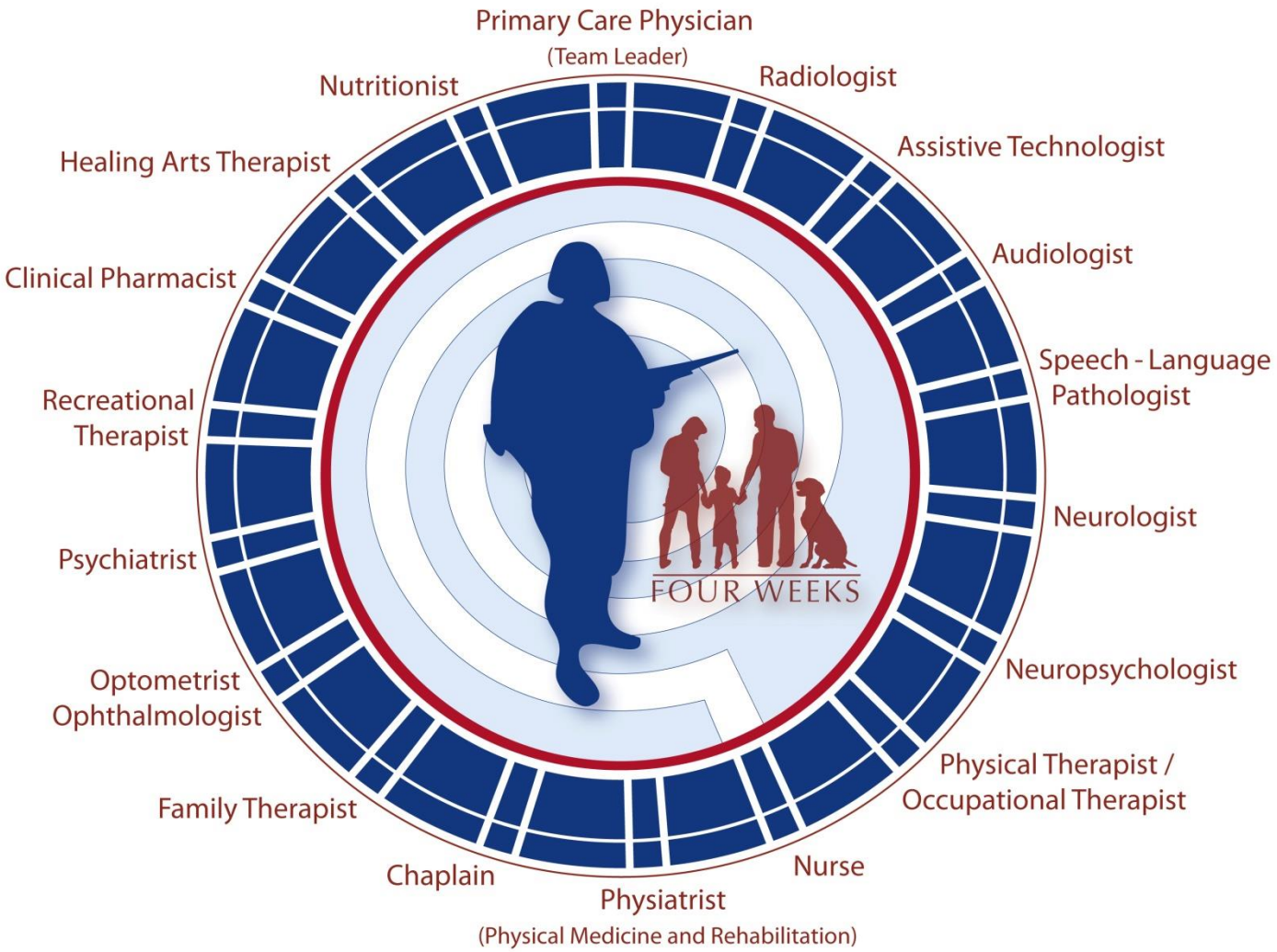


Patients by TBI Severity, n=115



*Includes multiple diagnoses per patient (totals to greater than 115)
**Other diagnoses reported by referring providers include ADD, cognitive disorder, combat stress, conversion disorder, mood disorder, psychosis, stuttering, suicidality
^Data not found on referral form manually mined from AHLTA notes: 6 patients had mTBI, 2 patients had mTBI/modTBI
^^Data not found on referral form manually mined from AHLTA notes: 5 patients had PTSD and of these five patients one was noted to also have a Cognitive DO NOS; 1 patient did not have a recorded Psychiatric note and 1 patient did not have a Psychiatric Dx noted in their record
Source of Data: NICoE Referral Forms

Collaborative, Patient-Centered Evaluation and Assessment



Reduce Suffering, Instill Hope, and Address Moral Injury

The NICoE Approach systematically targets specific areas of focus:

Goal Set 1

~ Day 1 and throughout program

- Ensure Safety
- Improve Sleep
- Decrease Physical Pain
- Decrease Psychological Pain
- Decrease Moral/Ethical Pain
- Facilitate Positive Use of the Health Care System/Restore Trust in the System

Goal Set 2

~ Day 1 – 4 and throughout program

- Intensive/Integrative Diagnoses
- Decrease Polypharmacy
- Self-Awareness – patient and family centric approach to understand problems preventing recovery
- Establish Goals for recovery

Goal Set 3

- Enhance Self-Management/Self-Efficacy
- Improve Relationships (family, chain of command, peers)
- Improve Functional Cognitive Performance
- Improve Psychosocial Functioning
- Improve Physical Performance

Typical NICoE Evaluation and Treatment Activities

While at NICoE, the SM is evaluated by

- Nursing
- Internal Medicine/Family Medicine
- Neurology (including EEG prn)
- Sleep Neurology (including Actigraphy, PSG)
- Psychiatry
- LCSW (Family therapist)
- Art Therapy
- Spirituality
- Physical Therapy including NeuroCom, CAREN
- Neuropsychology
- Occupational Therapy including Visual Perceptual Evaluation, Assistive Technologies
- Speech Language Pathology
- Optometry
- Audiology/Vestibular Evaluation
- Nutrition
- Radiology (MRI, PET/CT of the brain)
- Other consultations as needed

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- Speech Language Pathology
- Optometry
- Audiology/Vestibular Evaluation
- Nutrition
- Radiology (MRI, PET/CT of the brain)
- Other consultations as needed

Additional interventions include

- BOTOX
- Nerve Blocks, Trigger point injections
- Acupuncture
- Cupping/Scraping
- Biofeedback
- Heart Math
- Autogenic Training
- Frequency Specific Microcurrent
- Comprehensive Soldier Fitness-PREP
- Mind-Body Skill building
- Group therapy
- Education course
- Journaling
- Bibliotherapy
- Positive psychology
- Neurofeedback
- Recreation therapy
- Animal Assisted Therapy
- Laughter and Humor

Sample patient encounters across a four week stay (19 weekdays / 104 clinician encounters)

Week 1

- Introduction to NICoE
- Interdisciplinary Intake
- Pre-NICoE Assessments Review
- Vitals, Med Rec/InterD Meet
- Alpha Stim
- Pharm D
- Audiology
- Sleep, Neuro, IM, Pain Intervention
- Introduction to TBI
- Psychiatry Eval
- Interdisciplinary Working Group
- Family Eval
- Neuropsychology Interview
- Psychotherapy Group
- Sleep Education/Receive Actigraphy
- Optometry
- Intro to Wellness
- Creative Arts Therapy: Mask-Making
- Pain intervention and Meet with Nurse
- Brookville, Including Intro to Nutrition
- Psychotherapy Group

Week 2

- OT
- CSF-PREP: Foundations
- SLP 1
- Psychotherapy Group
- TBI MRI
- CSF-PREP: Building Confidence
- SLP 2
- Psychotherapy Group
- Interdisciplinary Working Group
- Neuropsych 1
- Creative Arts Therapy: Writing
- Psychotherapy Group
- Psych Health Meeting
- Radiology Rounds/Rehab Breakout Team
- Safe Substance Use
- CSF-PREP Goal Setting
- Rec Therapy Event

Week 3

- Managing Triggers
- Overview of Cognitive Distortions
- Meet with Nurse
- Psychiatry Follow Up
- CSF-PREP: Attention Control
- IM follow Up
- CSF-PREP: Energy Management
- Meet with Nurse
- Creative Arts Therapy: Collage
- PET CT
- Understanding Psychological and Emotional Health
- CSF-PREP: Individual Session
- Managing Triggers
- Family Meeting
- Psychotherapy Group
- PT HEP
- Occupational Functioning
- PT CAREN
- Safe Substance Use
- Occupational Funcitoning Community Reintegration Program

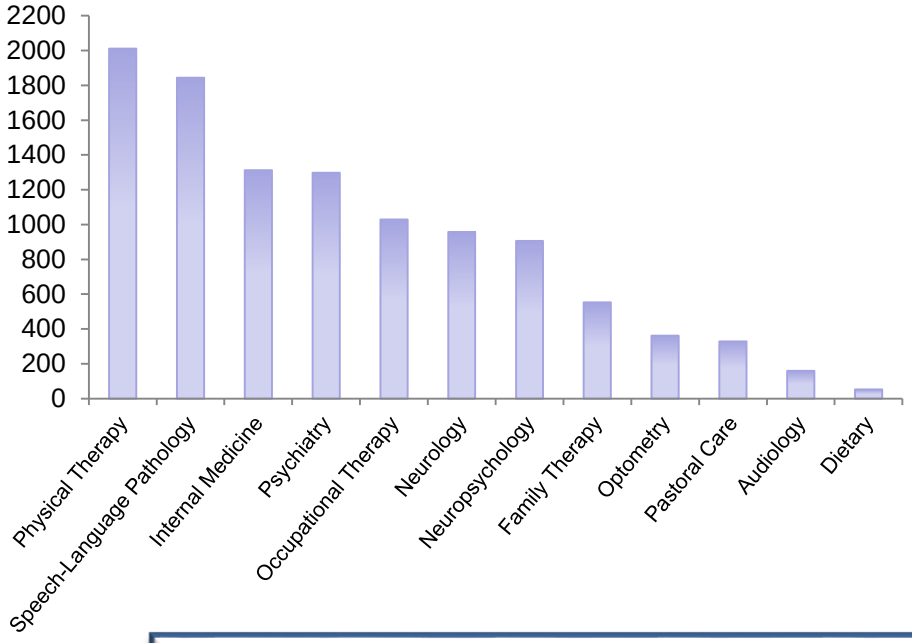
Week 4

- Psychotherapy Group
- Psychiatry Follow Up
- Pharm D Follow Up
- Practical Healthy Eating
- CSF-PREP: Integrating Imagery
- PT HEP
- Managing Triggers
- Self-Advocacy in the Treatment and Recovery Process
- PT HEP
- Interdisciplinary Working Group
- Psychotherapy Group
- PT HEP
- Family Meeting
- Wellness Breakout Meeting
- Safe Substance Use
- CREDO/Commencement
- D/C Meeting
- Psych Health Meeting
- Radiology Rounds
- Rehab Breakout Meeting

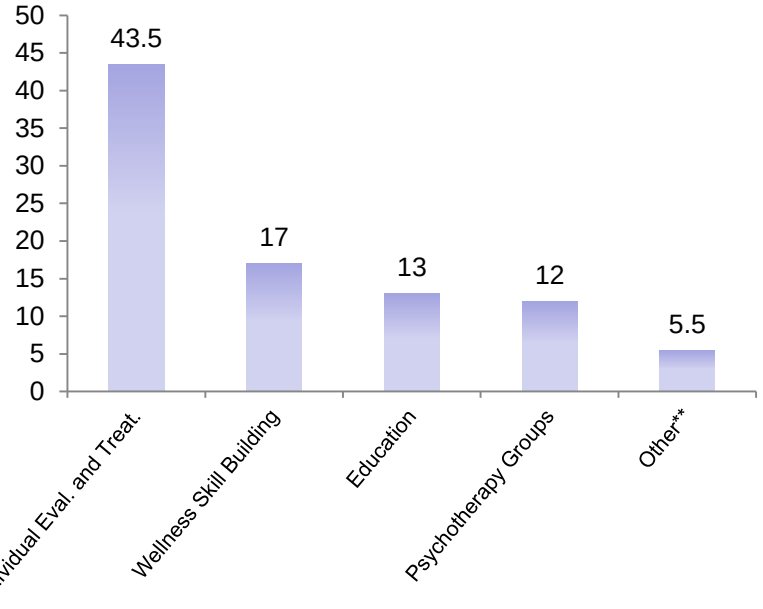
NICoE Patients

Encounters by Provider Specialty and Clinical Program Hours

Encounters by Provider Specialty* (>10,000)



Average Hours per Clinical Program per Patient



Of the 115 patients referred to NICoE between October 2010 and June 2011:

- Collectively, cohort patients logged >10,000 encounters with NICoE providers
- Each patient participates in over 90 hours of program activity during their stay
- The NICoE's three-week clinical program includes individual evaluation and treatment, wellness skill building, education, and psychotherapy groups

*Excludes nursing and assistive techs

** Includes Physical Rehabilitation Therapy/Rec Therapy, Nutrition, and Mind/Body Skills Training

Source of encounter data: AHLTA and CHCS

Observed Mask-Making Themes

Patriotism

The Injury

Death/Grief

Warrior Canine Connection

NICoE Clinical Evaluations

- The following six clinical evaluations are performed pre- and post-NICoE treatment:
  - Satisfaction with Life Scale (SWLS)
  - Neurobehavioral Symptom Inventory (NSI)
  - Epworth Sleepiness Scale (ESS)
  - PTSD Check List-Military (PCL-M)
  - Dizziness Handicap Inventory (DHI)
  - Headache Impact Test (HIT)
- Each of these evaluations have demonstrated quantitative improvement, including a patient satisfaction score of 90% through July 2013

Post-NICoE Patient Satisfaction Survey,

Patient Satisfaction Portion

Scores by Question; n = 261

Section	% Satisfied	
Overall	Overall satisfaction score	**99%**
	The likelihood of recommending the NICoE to others	**99%**
Self Advocacy	You have a better understanding of your strengths and weaknesses than prior to your NICoE visit	**95%**
	You feel you have the skills to actively engage in your recovery	**94%**
	You feel confident that the follow-up treatment plan can be continued at your home command	**64%**
	You feel more confident to express your health needs with other healthcare providers	**85%**
Admission and Discharge	Information was given to you about the NICoE program and what to expect prior to your arrival	**78%**
	Telling your story in a team setting was preferable than in your individual appointments	**75%**
	The program was the right length of time for you	**56%**
	The discharge/treatment plan reflected input from everyone on your team	**97%**
	What you learned during your stay at NICoE and your discharge plan were consistent	**97%**
	If the program was NOT the right length of time, would you have preferred longer, shorter	**Longer: 128; Shorter: 10**
Wait Time and Appointment Schedule	You felt your daily schedule was kept at a good pace	**90%**
	Your wait time for appointments was minimal	**95%**
	Your wait time for test results was acceptable	**91%**
Education*	The Group Education series has increased my knowledge about TBI and Psychological Health	**83%**
	The Group Education series provided knowledge and skills I will be able to use when I leave NICoE	**88%**
	The number of classes in the Group Education series were TOO FEW, JUST RIGHT, TOO MANY	**Too few: 2; Just Right: 16; Too many: 3**
Environment	The facility was neat and clean, and it was easy to find your way to appointments	**99%**
	You felt comfortable and safe, and you felt you had privacy	**98%**
Staff	Listened to you	**98%**
	Took enough time with you	**99%**
	Explained what you want to know	**98%**
	Gave you good advice and treatment	**99%**
	Were friendly and helpful	**100%**
	Answered your questions	**98%**

Source of Data: Post-NICoE Patient Satisfaction Survey; Timeframe = September 2011 through September 2013; *Education section added July 2013

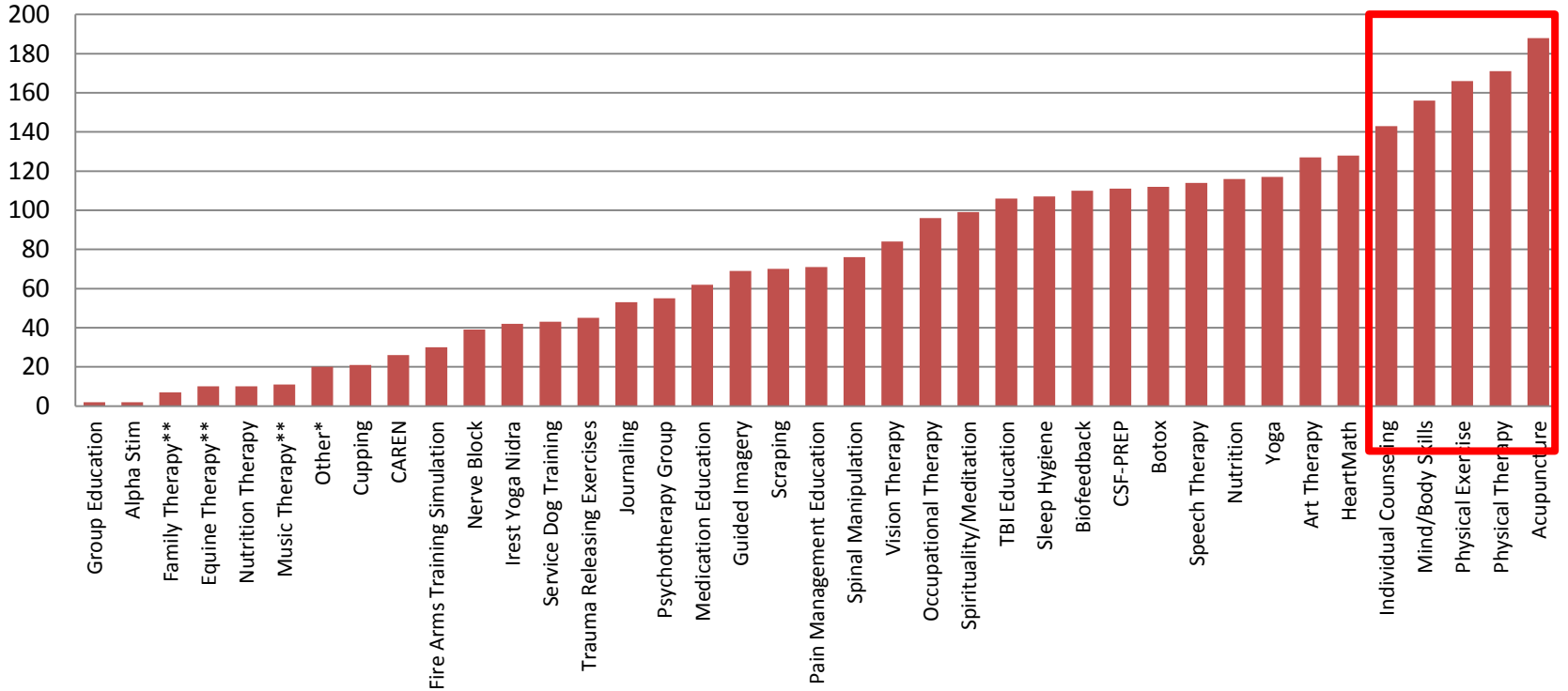
Post-NICoE Patient Satisfaction Survey,

Post-NICoE Portion

"Please indicate which techniques or tools you would like to **continue** if made available."

Count of individuals that selected each technique or tool

n = 257



Source of Data: Post-NICoE Patient Satisfaction Survey; Timeframe = September 2011 through September 2013

*(Other: Aqua therapy, Deep tissue massage, Sobriety, Neurofeedback, FSM, Lisa's techniques, Reiki, Vestibular rehab, Cognitive skills, Nesting, Chiropractor, Contact with CAPT Koffman, Cranial Sacral Therapy, Tai Chi, Recreational therapy)

** Added to surveys in July (therefore a lower N)

How Effective is NICoE? (Clinical)

Outcome Measure	n	Admission Mean (Standard Deviation)	Discharge Mean (Standard Deviation)	p-value
Satisfaction with Life (SWLS) *	181	3.98 (1.84)	4.65 (1.67)	.000
Neurobehavioral Symptom Inventory (NSI)	178	46.04 (16.90)	35.13 (17.99)	.000
Epworth	181	10.38 (6.08)	9.31 (5.60)	.002
PCL-M	179	55.08 (15.59)	44.25 (18.33)	.000
Dizziness Handicap Inventory (DHI)	47*	44.62 (28.25)	37.11 (29.10)	.000
Headache Impact Test (HIT)	182	61.87 (8.15)	58.01 (8.72)	.000
Neurobehavioral Symptom Inventory (NSI) score for Headaches	115	3.10 (.816)	2.81 (.760)	.001

Data collected June 2011 – November 2012

*Satisfaction with Life scores reflect response for question 3: “I am satisfied with my life.”
*The NICOE only administers the DHI to patients who present with dizziness as a symptom.

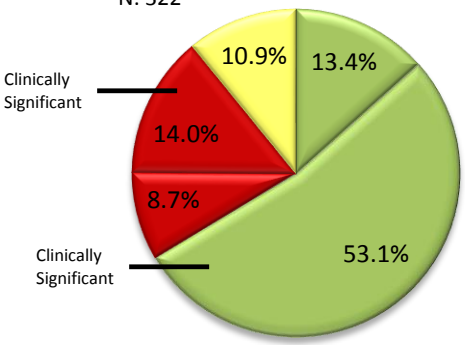
Overview of Outcome Measures

July 2011-December 2013

The charts below reflect score changes between admission and discharge across six NICoE outcome measures

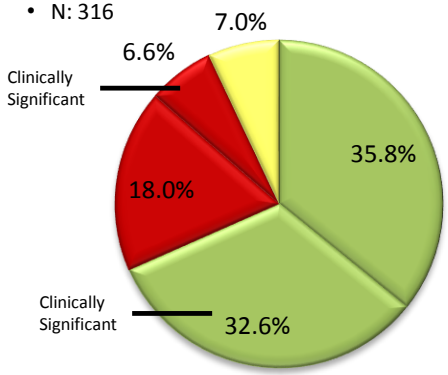
Headache Impact Test (HIT-6)

- 6 items
- Possible score range: 36-78
- N: 322



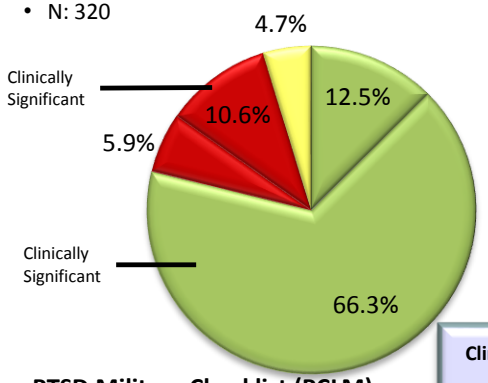
Satisfaction With Life Scale (SWLS)

- 5 items
- Possible score range: 5-35
- N: 316



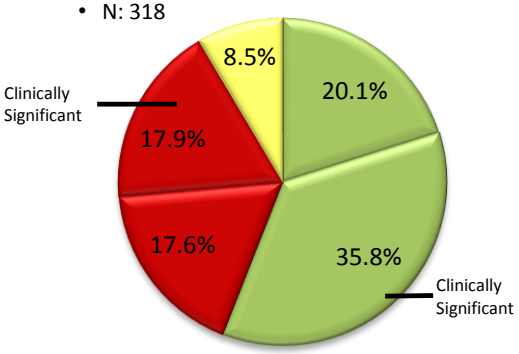
Neurobehavioral Symptom Inventory (NSI)

- 22 items
- Possible score range: 0-88
- N: 320



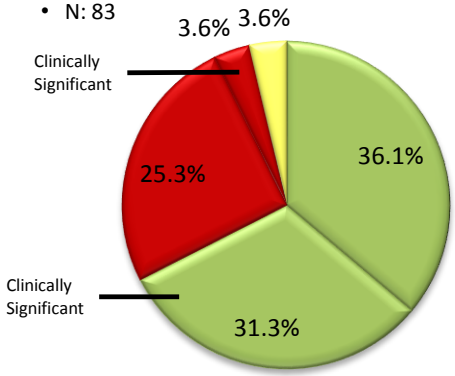
Epworth Sleepiness Scale

- 8 items
- Possible score range: 0-24
- N: 318



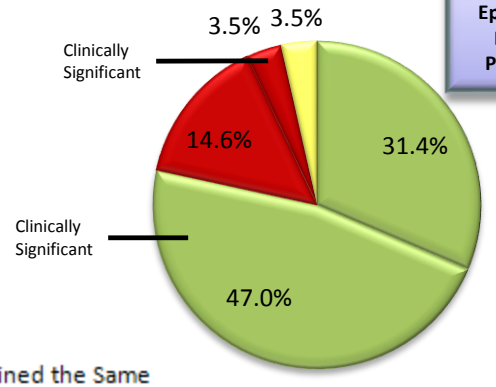
Dizziness Handicap Inventory (DHI)

- 25 items
- Possible score range: 0-100
- N: 83



PTSD Military Checklist (PCLM)

- 17 items
- Possible score range: 17-85
- N: 315



Clinical Significance Key*

HIT: 2.3 point Δ
SWLS: 5 point Δ
NSI: 5 point Δ
Epworth: 3 point Δ
DHI: 18 point Δ
PCLM: 10 point Δ

Interpretation of results:

- Improved | Clinically Significant Improvement* | Worsened | Clinically Significant Worsening* | Remained the Same
- *Improvement is determined by any point change greater than 0 signifying a lessening of symptoms. The remained the same category consists of scores that did not change between admission and discharge. Worsening is determined by any point change greater than 0 signifying an increase in symptoms.*

Current and Long-Term Outcome Primary Clinical-Research Platform

= Current Collection Points

= Long-term Collection Points

		NICoE Admit	NICoE D/C	Post-NICoE 3 Month	6 Month	12 Month	24 Month
Current Measures	1. Satisfaction with Life Scale	✓	✓		✓	✓	✓
	2. Neurobehavioral Symptom Inventory	✓	✓		✓	✓	✓
	3. PCL-M (PTSD Checklist – Military)	✓	✓		✓	✓	✓
	4. Epworth Sleepiness Scale	✓	✓		✓	✓	✓
	5. Dizziness Handicap Inventory	✓	✓		✓	✓	✓
	6. Headache Impact Test	✓	✓		✓	✓	✓
	7. Medications	✓	✓	✓			
	8. Current Military Status	✓		✓	✓	✓	✓
	9. Interactions with the Legal System	✓		✓	✓	✓	✓
	10. Marital Status	✓		✓	✓	✓	✓
Additional Measures	11. Education Status			✓	✓	✓	✓
	12. Employment Status			✓	✓	✓	✓
	13. Financial Hardship			✓	✓	✓	✓
	14. Unanticipated Visits			✓	✓	✓	✓

Measures noted in red are currently collected by the DVBIC RCC database

*NICoE RCC will call patients within 3-7 days after discharge and, if necessary, 1 month after discharge to ensure coordination of care with home station

Best/Promising Practices with PTSD and TBI

The NICoE approach is a strategy that facilitates a shift in the way providers approach a patient's care. The approach utilizes multiple avenues of evaluation and treatment to maximize the experience and mitigate potential pitfalls. Characteristics include:

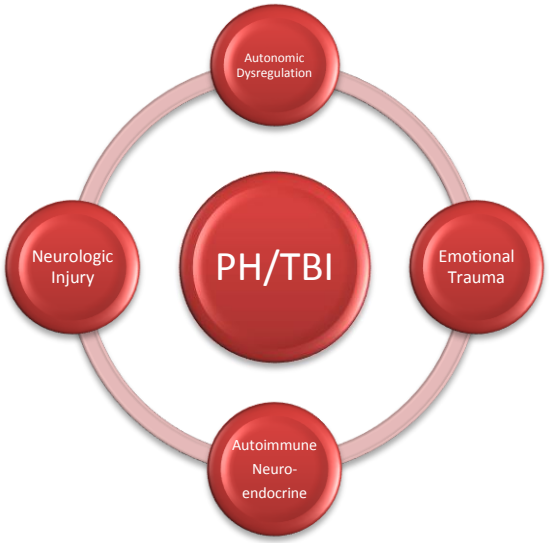
- ***Interdisciplinary Team Model***
- ***Patient and family centered holistic care***
- ***Timely sequenced care***
- ***Empowerment of the patient through skills based education***
- ***Emphasis on improved patient outcome over throughput***

NICoE Clinical Research Strategy

- Standardized Interdisciplinary Intensive Outpatient Program to evaluate and treat mTBI/PH
  - Leveraging subspecialized equipment, integrative medicine and innovative therapies
  - Framework to support a large clinical research database and hypothesis development
- Alignment with National Research Action Plan
- Advanced informatics that integrates with CNRM and FITBR
  - Collect 2,000 clinical data elements per patient
  - Collect 41,000 imaging data elements per patient
- Robust Research Platform
  - 17 active internal protocols
  - 6 active external protocols
  - Current 12 Federal and 6 Academic Partners (including WRNMMC, USU, DVBIC, WRAIR/NMRC, NIH)

Research Strategy Aligned with National Research Action Plan

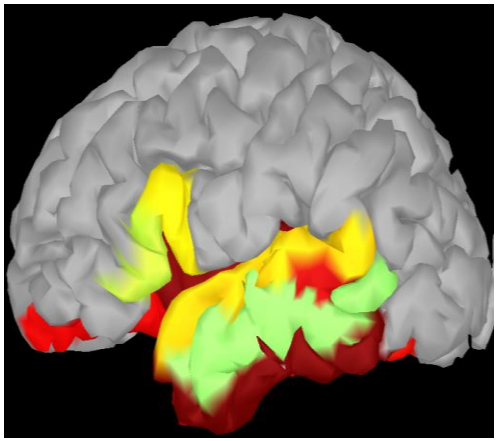
Classification & Staging*



Multi-Dimensional analytics for subpopulation identification

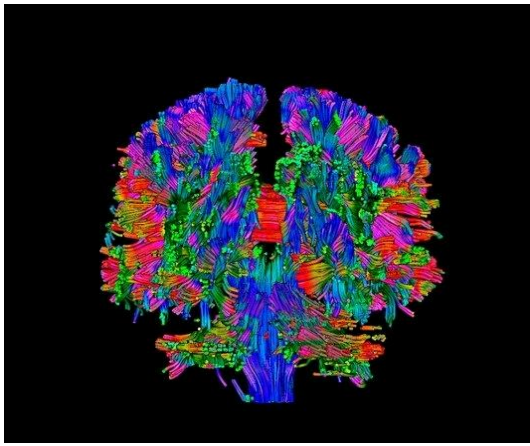
Precision in Neural Network Disruption

Pathophysiology and Response to Treatment*



Anatomic and biological response to stressors and treatment.

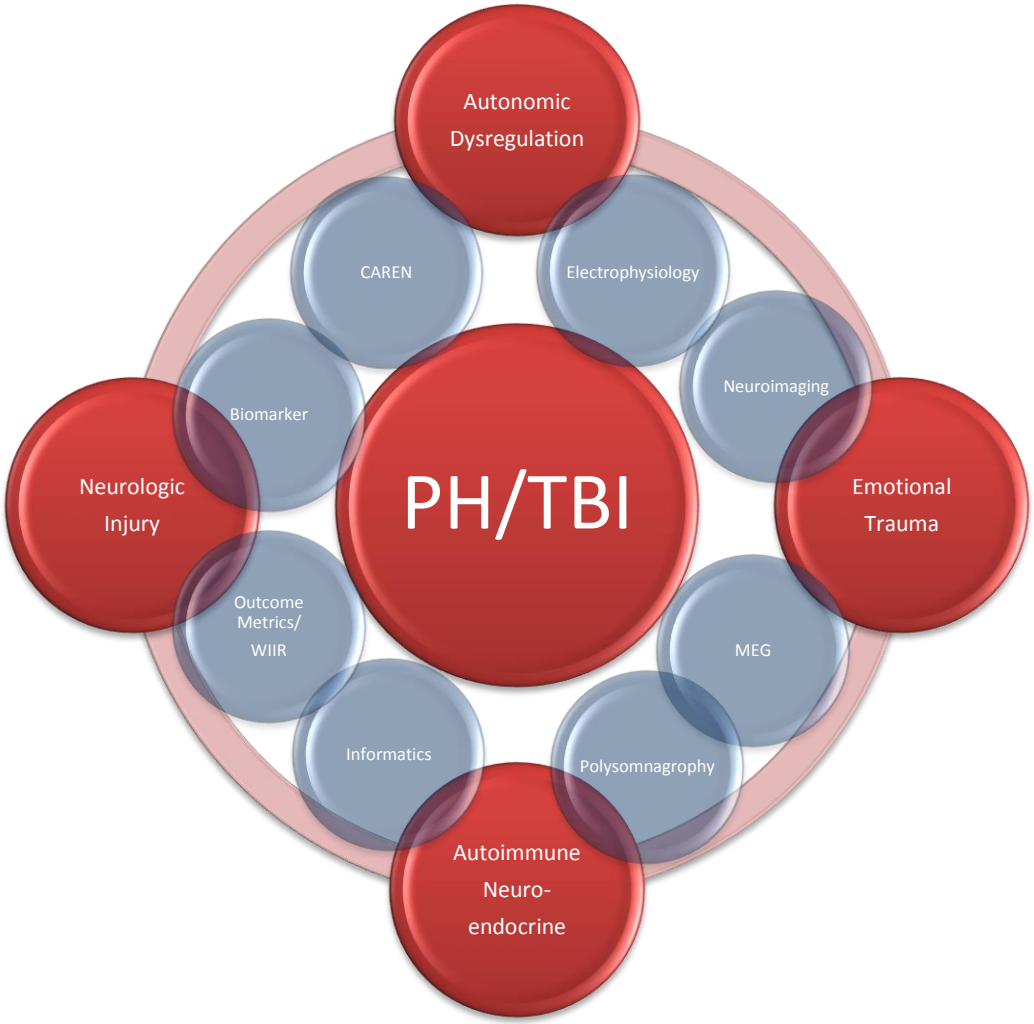
Chronic Effects of TBI*



Population surveillance of chronic degeneration (e.g.CTE) and functional life

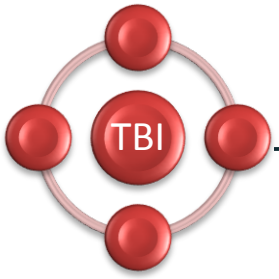
*Based on NRAP gap analysis

Classification of Co-Morbidity

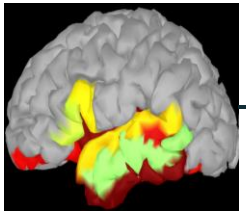


NICoE Research Protocols

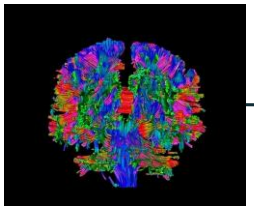
Classification



Response



Surveillance



- MEG/EEG
- MEG Core
- Datamart
- Imaging Core
- Brain Indices
- [illegible]
- VR and IE
- Predictors of PTSD
- HBOT
- [illegible]
- Walking and Tasking
- Eye Tracking
- TMS for PTSD/TBI
- DANA
- Team TBI
- Harvard Epigenetics
- DVBIC 15 Year
- VIrTICO-bp VR

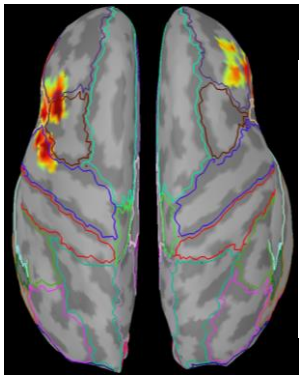
Academic Partnerships: Research at NICoE

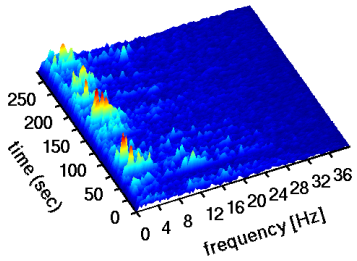
- Current efforts
  - Despite hiring freeze and budget constraints, the following has been accomplished:

Articles in Peer-Reviewed Publications	**Poster/ Podium Presentations**	***Number of Active Studies***			
		# Active Protocols	*# in IRB Review*	*# Submitted for Funding*	*# Under Development*
13	24	13	3	8	6

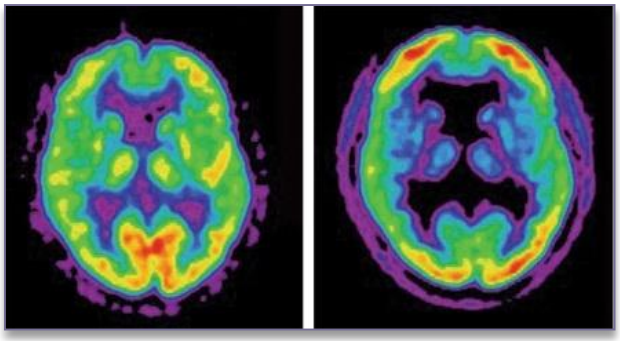
- Challenges:
  - No current budget for research
    - Lack of dedicated funding impedes development of research projects and recruitment of qualified research staff
    - Eight NICoE research positions will end 30 August due to insufficient funding
  - Need to partner with other academic institutions

Major Diagnostic and Rehabilitation Equipment

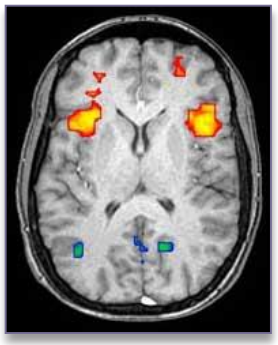




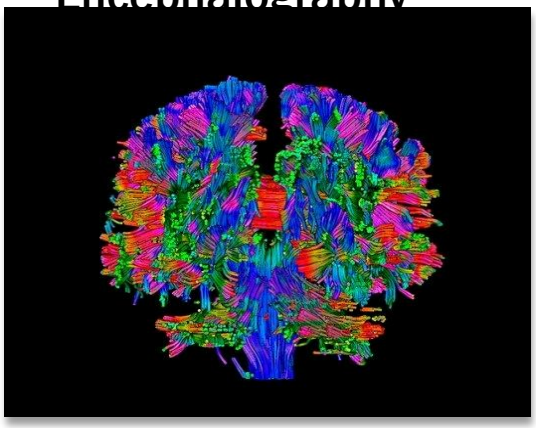
Magneto Encephalography



Positron Emission Tomography with Computed

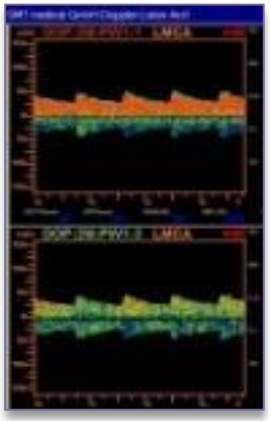


MRI (3-T) / Functional MRI



Diffusion Tensor Imaging (DTI)

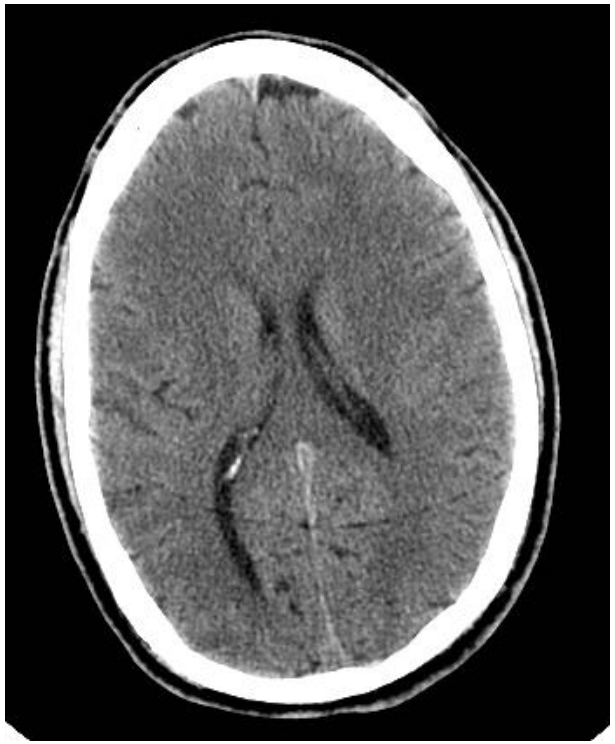
CAREN (Computer Assisted Rehabilitation Environment) system



Trans-Cranial Doppler Ultrasound

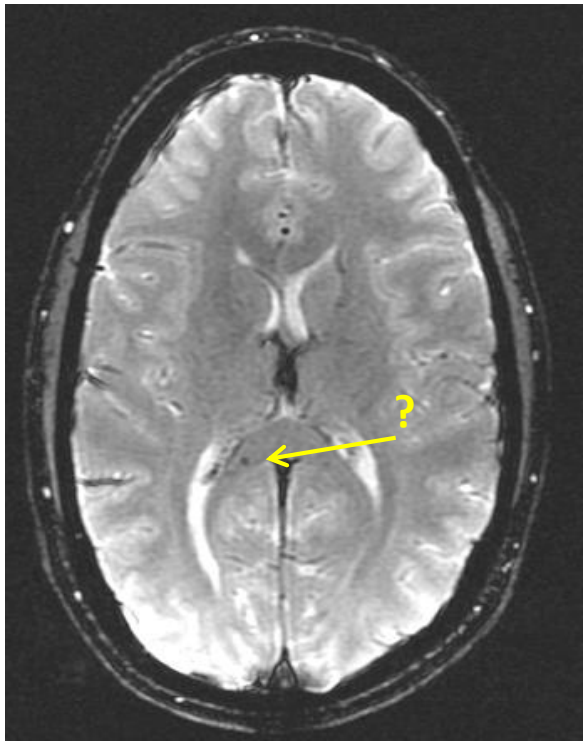
MRI Findings

CT



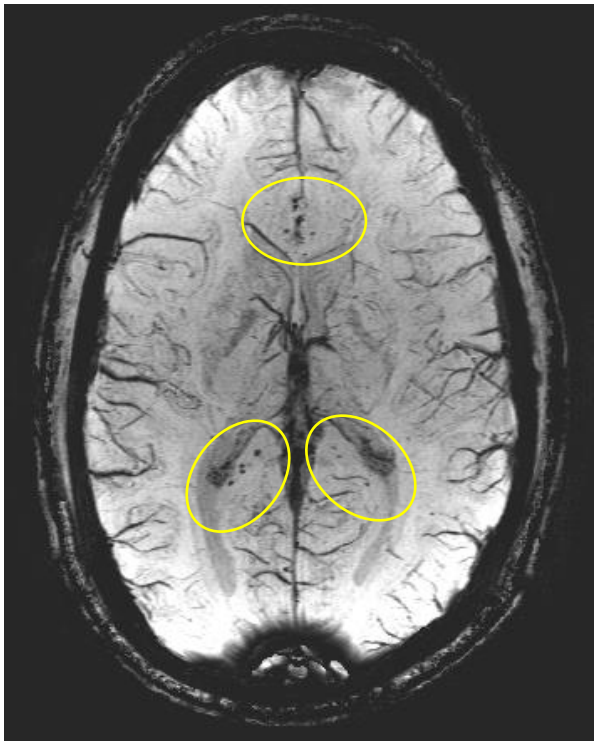
Read as Normal

Routine MRI- GRE



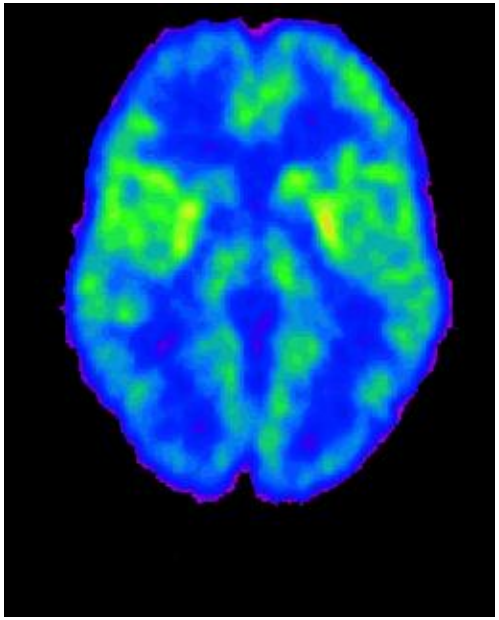
Possible Lesion
Corpus Callosum

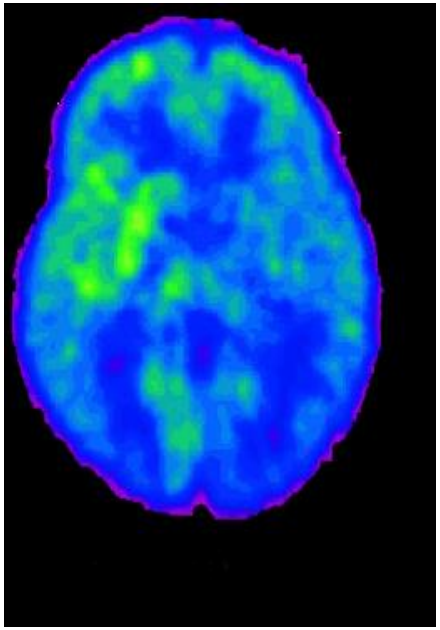
New TBI Study- SWI

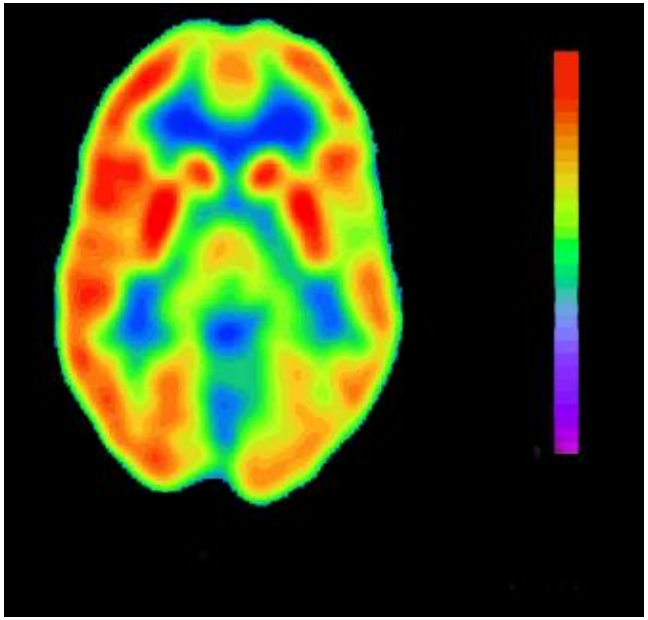


Multiple Lesions Detected

Mild GCS 15 **Severe GCS 5** **Normal**

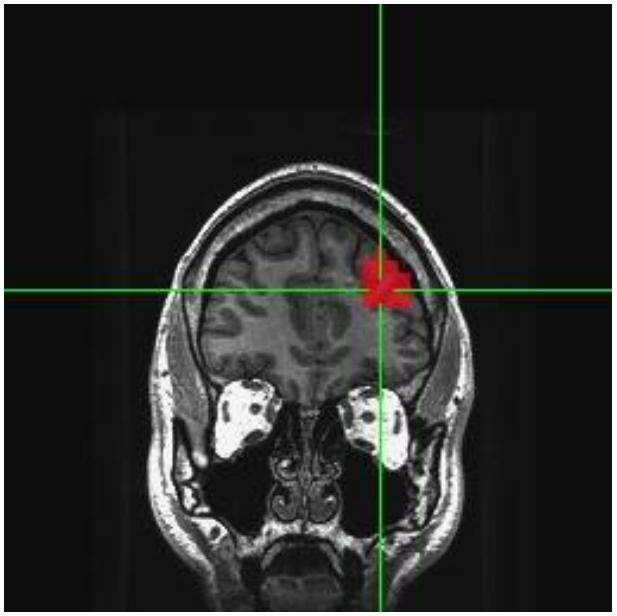




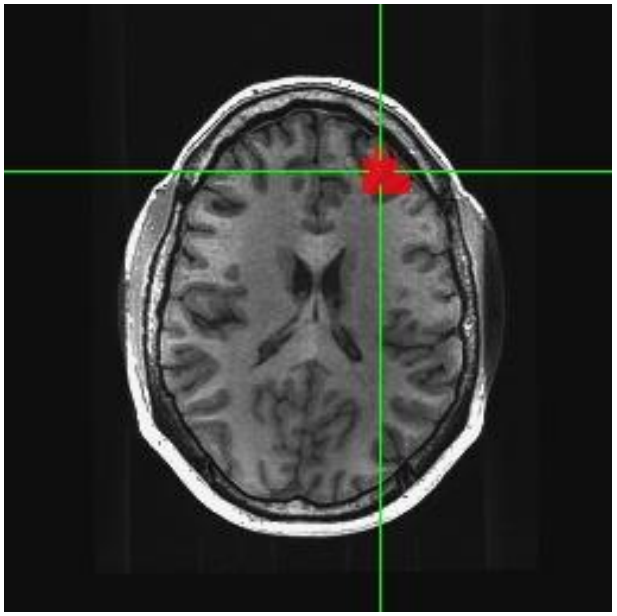


An Imaging Biomarker of MTBI ?

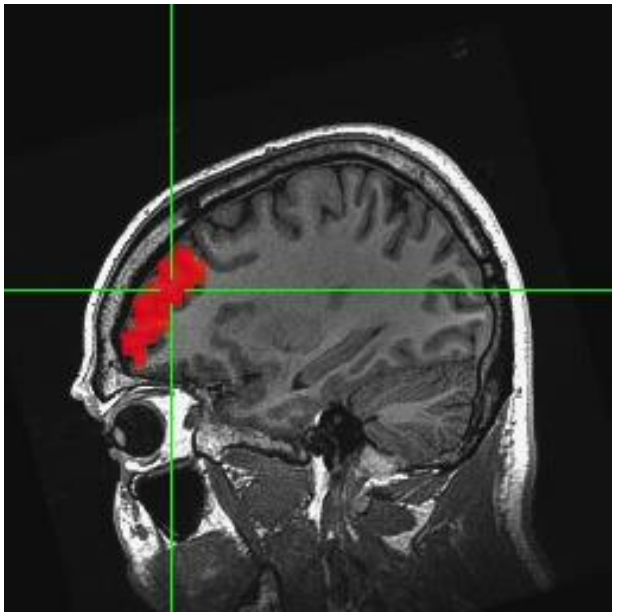
NICoE MEG Patient – Slow wave activity (1 – 4 Hz)



Coronal

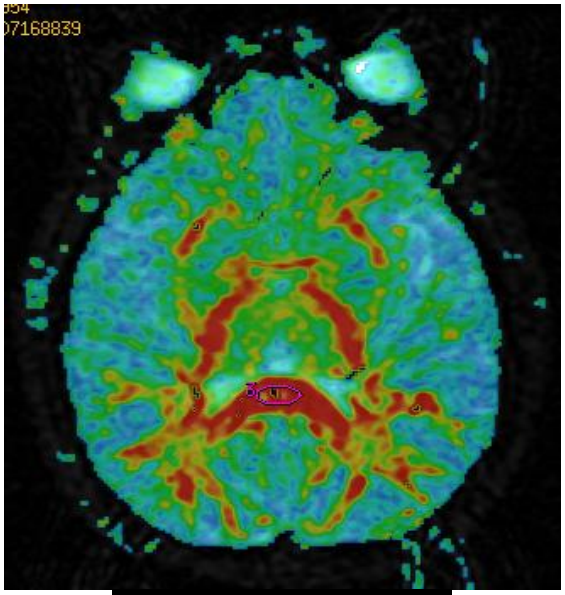


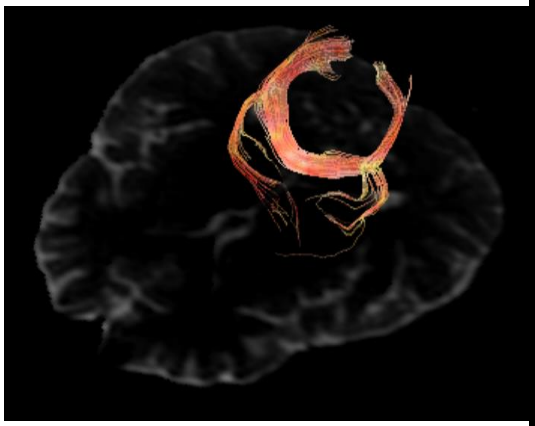
Axial

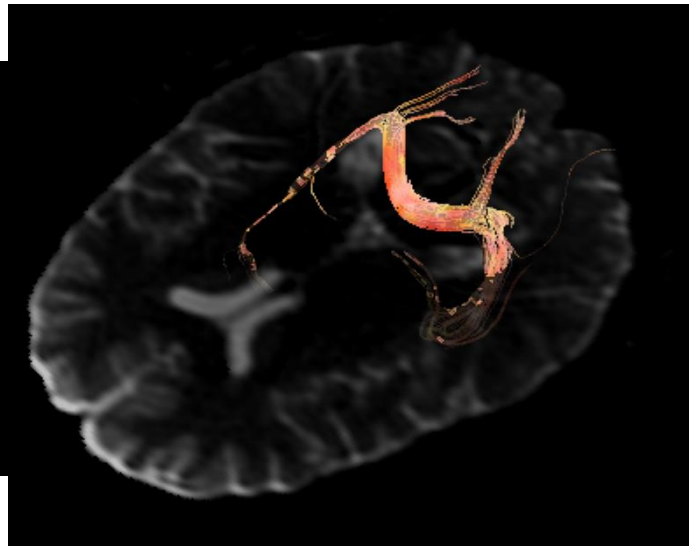


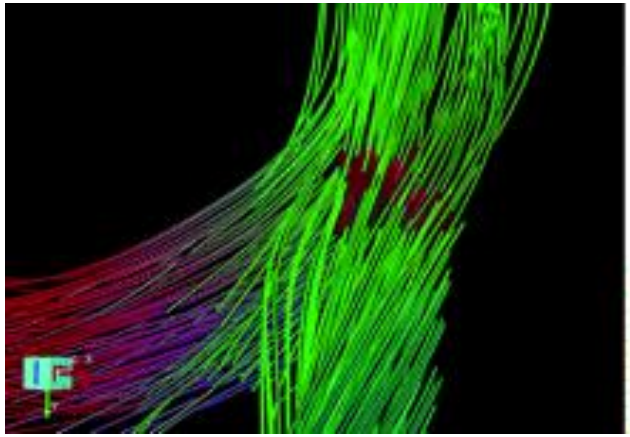
Sagittal

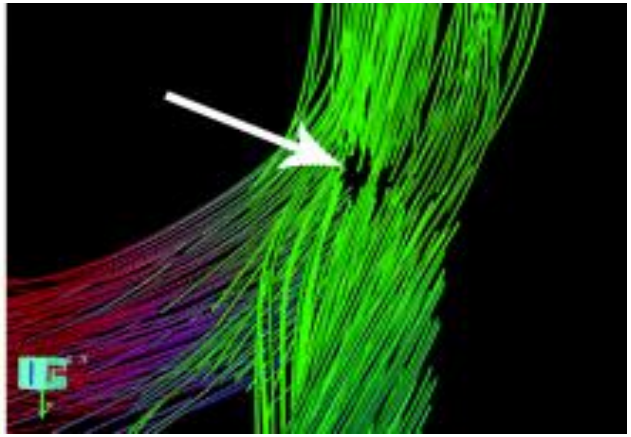
Corpus Callosum



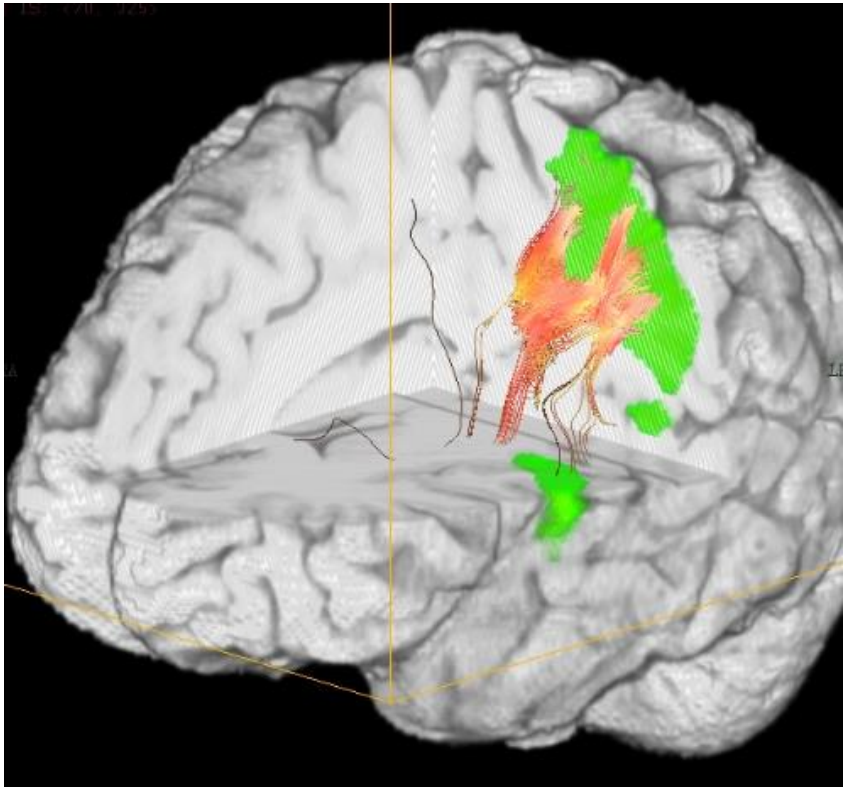


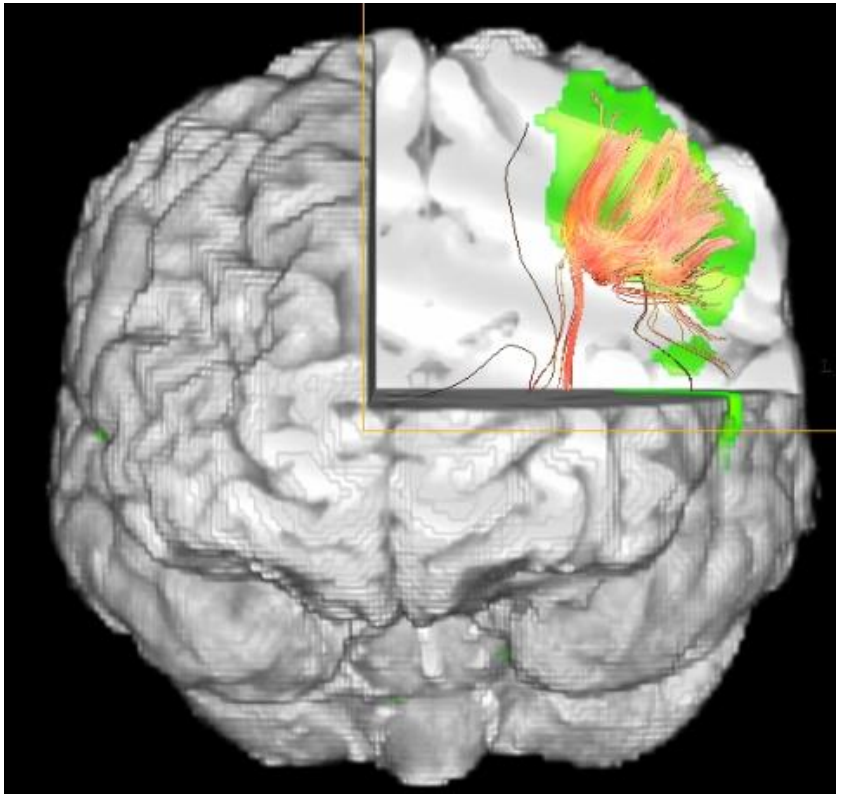






Functional Connectivity





Characterization of T2 Hyperintensity Lesions in Patients with Mild Traumatic Brain Injury

Jesus J. Caban[1], Savannah A. Green[2], Gerard Riedy[1]

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National Capital Neuroimaging Consortium

Abstract

Mild traumatic brain injury (TBI) is often an invisible injury that is poorly understood and can be difficult to diagnose. Recent neuroimaging studies on patients diagnosed with mild TBI (mTBI) have demonstrated an increase in hyperintense brain lesions on T2-weighted MR images. We perform an in-depth analysis of the multi-modal and morphological properties of T2 hyperintensity lesions among service members diagnosed with mTBI. A total of 790 punctuate T2 hyperintensity lesions from 89 mTBI subjects were analyzed and used to characterize the lesions based on different quantitative measurements. Morphological analysis shows that on average, T2 hyperintensity lesions have volumes of 23mm^3 (±24.75), a roundness measure of 0.83 (±0.08) and an elongation of 7.90 (±2.49). The frontal lobe lesions demonstrated significantly more elongated lesions when compared to other areas of the brain.

Introduction

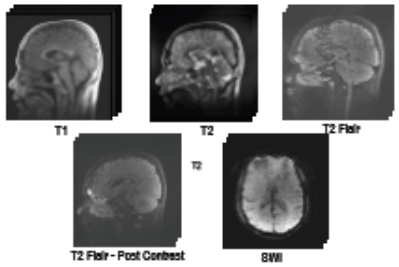

Figure 1: Different MRI image modalities of the same subject.

- Magnetic resonance imaging (MRI) and many of its imaging sequences such as T1, T2, T1+C, T2-Flair, SWI, and GRE are currently the preferred way to evaluate brain abnormalities caused by injuries.
- Recent neuroimaging studies on patients diagnosed with mild TBI have indicated an increase in hyperintensity brain lesions on T2-weighted MR images.
- Despite advances in technologies, the characteristics of T2 hyperintense lesions vary from one patient to the next, thus making the classification of lesions a very difficult task.

Method

- A collection of 197 MRI studies of service members diagnosed with TBI was obtained. Each study was reviewed by an expert neuroradiologist who also annotated the slices where T2 hyperintensity lesions were present. T2 hyperintensity lesions were found in 56.12% of the TBI patients.
- A total of 89 patients were found to have mild TBI, punctuate T2 hyperintensity lesions, and images without motion artifacts.
- Prior to extracting quantitative measurements of the lesions from the 89 studies, a series of preprocessing steps were performed.
- Processing:
  1. The expert's annotations were refined to guarantee accurate masks and consistency across studies.
  2. A computer-based application performed a set of morphological and histogram-based operations to accurately estimate 3D masks.
  3. T2 lesion masks were used to extract quantitative measurements of the morphological properties of each lesion. A total of 790 punctuate T2 hyperintensity lesions were analyzed.

Results

- Once quantitative image features were extracted for each lesion, an in-depth analysis of their multi-modal and morphological properties was done.
- On average, 6.56 lesions were found per patient with most patients having 1-3 lesions, but some having as many as 90 punctuate WMH lesions.
- Our results show that on average T2 hyperintensity lesions in TBI have volumes of 23mm^3 (±24.75), a roundness measure of 0.83 (±0.08) and an elongation of 7.90 (±2.49). The volumetric size of punctuate T2 hyperintensity lesions shows a large variance mainly due to outliers.
- An in-depth analysis shows that 98.4% of the punctuated lesions are between 10–100mm^3 and have a 95% confidence average of 19.65mm^3 (±12.35). The roundness measure shows that most non-specific T2 hyperintensity regions follow a circular/round shape.
- The elongation measurements show that despite most lesions being round, many tend to be elongated toward a particular direction.

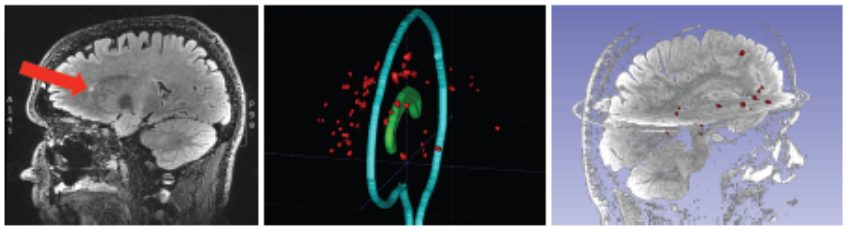

Figure 2: (left) Illustration of a T2-hyperintensity lesions. (center) 3D annotations of a service members with a significant amount of T2-hyperintensity regions. Most T2 hyperintensity regions were located within the frontal lobe of the brain. (right) 3D annotations of a service members with about a dozen punctuate T2 lesions.

Results (cont.)

- When combining elongation with location we found that frontal lobe T2 lesions have an average elongation of 8.04 units while lesions of other areas of the brain has a measure of 7.58 units. That difference is significant (t = 2.40, p=0.016) and can be used to better characterize different T2 lesions.

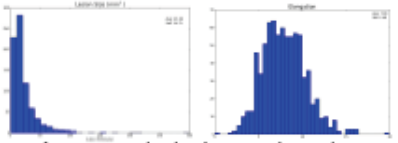

Figure 3: (left) Lesion size (right) Elongation of lesions

Descriptive Statistics

FRONTAL	N	Mean	Std. Deviation	Std. Error Mean
FRONTAL	541	8.04	2.48	0.10
NOT FRONTAL	249	7.58	2.49	0.16

Comparison between Frontal and Non-Frontal Lesions

F	t	Sig. (2-tailed)	Mean Difference
0.065	2.40	0.016	0.46

Conclusion

In order to characterize the brain pathology of combat veterans and individuals with blast-related mTBI, we need to better characterize the most common lesions that are identified in these subjects on MRI, non-specific T2 hyperintensity lesions. In this paper we presented a method to extract quantitative morphological properties of the lesions and demonstrate how those features can be used to understand the characteristics of white matter T2 lesions.

References:

[1] Spit et al. (2005). Age-related changes in normal-appearing brain tissue and white matter hyperintensities: More of the same or something else? *American Journal of Neuroradiology, 26*(4), 725-9.

[2] Taber et al., (2006). Blast-related traumatic brain injury: What is known? *The Journal of Neuropsychiatry and Clinical Neurosciences, 18*(2), 141-5.

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E: jesus.j.caban.civ@health.mil

Heterogeneity in the TBI subject population in response to a Go/NoGo task

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2 National Intrepid Center of Excellence (NICoE), Bethesda, MD

Contact e-mail: jennifer.evans@nih.gov

INTRODUCTION

- A prominent clinical feature in traumatic brain injury (TBI) is behavioral impulsivity (Okie, 2005) suggesting impairment of frontal inhibitory control processes.
- This study investigated differences in fMRI responses between a cohort of military mild TBI patients and controls in a mixed inhibitory Go/No-Go stroop task (described below).
  - The Stroop task has been used to probe selective attention and has been found to have positive correlation with reported post concussive symptoms (Smits, 2009)
  - The Go/No-go task has been used to probe inhibitory control and TBI patients have shown increased response times (Azouvi, 2004)
- Much has been said about the heterogeneity of the injury, disease progression and symptom manifestation in these cases. We believe this should be reflected in the individual response patterns.
- We look at the heterogeneity of the responses in this population by applying a hierarchical clustering algorithm to the individual response maps from standard correlation analysis to see if there are naturally occurring subgroups of response patterns.
- This work will inform future group analyses and may have eventually aid in the classification of mTBI injuries and associated deficits.

METHODS

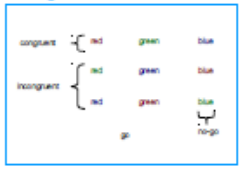
Participants:
- Sixteen (138) participants were recruited from USA military personnel at Walter Reed Army Medical Center (WRAMC) who had been recently injured in combat and categorized as having TBI.
- All but one of the patients suffered blast-related injuries due to exposure to an explosive device or weapon.
- Thirteen (13) control subjects were also recruited from military personnel at WRAMC who were on active duty but had not previously been deployed.

fMRI acquisition
- Imaging was carried out on a 3T Signa MRI scanner (General Electric, Milwaukee, WI) with a 32-channel head coil.The images were obtained using an echo-planar imaging (EPI)Sequence.
- A visual facial N-back task was presented to the subjects using a goggle system (Nordic NeuroLab Inc., Milwaukee, WI).

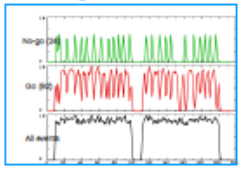
Go / No-go Task
- The paradigm involved the words displayed "red", "green", and "blue" variously displayed in red, green, or blue text.
- Subjects were to respond with a right button press to red, and left press to green and withhold response to blue.
- Events occurred at jittered intervals of 2 s.

Individual correlation analysis
- The event types were collapsed into go/nogo categories and there were 25 nogo events as the stroop effect for the blue non-response events showed negligible response time difference.
- Subjects with less than an 80% overall success rate were excluded from further analyses.

Paradigm schematic



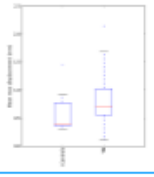
Event timing



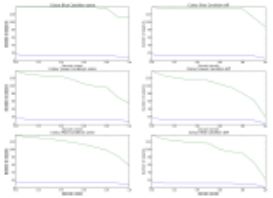
RESULTS

Motion

- The motion of the subjects in the analyses are shown below,
- No significant motion differences exist between these groups

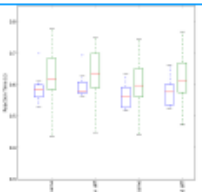


Response accuracy



The response accuracy curves for all the subjects in this study are shown above. A cutoff of 80% accuracy was used for further analyses.

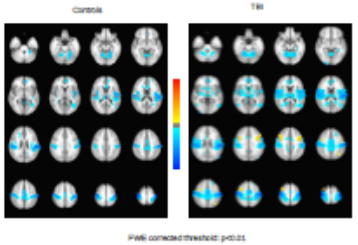
Reaction Times



- The reaction times for each response category are shown above
- TBI subjects have slightly longer times

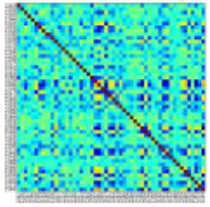
Group results

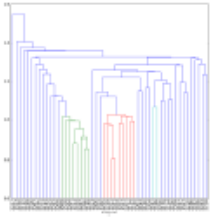
- The group average results using 3dMEMA (Chen, 2012) are shown to the right.
- 3DMEMA was used because it takes into account the variability of the subject response which should improve accuracy.
- Similar regions show responses in both groups
- Only a single region centered on the visual cortex shows a significant difference between groups.



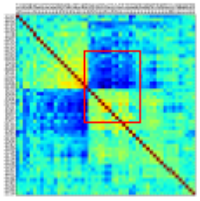
Hierarchical clustering of individual group map responses

- The correlation matrix (right) of all the of the individual TBI subjects' response maps (e.g. left) is generated by:
  - Linearizing and stacking each 45x58x49 spatial beta weight response matrix (as shown abov)
  - Correlating this matrix with itself to get the correlation of each subjects' map with the others in the study
- The matrix has 1's along it's diagonal consistent with perfect correlation of the subject with themselves.

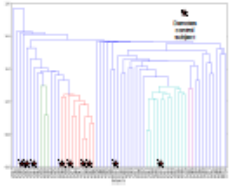




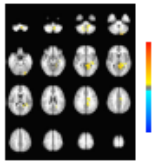
- The correlation matrix can then be hierarchically clustered according to the Euclidean distance between correlation lines for each subject resulting in the dendrogram graph to the left
- Subjects with similar response patterns should cluster together
- The correlation matrix can be reorganized to show the subject groupings according to the dendrogram as shown on the right.
- Subroups of TBI reponses emerge from the reorganized correlation matrix on the right



- To investigate the branching of the dendrogram the controls were added to the analyses (below) illustrating overlap of TBI and control subjects in terms of response similarity



- To investigate the differences between groups using the central 10 subjects within the red box above. The reaction times (bottom, left) and group differences (bottom, right) were calculated.
- A trend towards longer reaction times is suggested in the second group
- Significant regional differences are primarily found in the anterior and posterior cingulate.



DISCUSSION

- Task response times indicate that TBI subjects have slightly longer response times than controls. Some TBI subjects have response times that are considerably shorter than any controls, which may be worth further investigation.
- The lack of group differences in the standard group maps may be due to the heterogeneity of the TBI population or smaller number of controls.
- The heterogeneity of this data is similar to comments by Murphy (2004) who investigated the number of subjects needed to provide an accurate group map in a go/no-go task finding that 25 subjects yielded a stable group map in normal controls. Therefore the 58 TBI subjects used in this study should normally be sufficient while adding a few more control subjects would be ideal.
- However, hierarchical clustering of the individual TBI subject response maps revealed subgroupings of subjects, with each group containing ~20 subjects. Substantial differences may be observed between these subgroups. This could imply that these groups should be treated as separate TBI populations
- An extension of this work will be to look at the grouping of a second task both jointly and also separately to see if this information can be used to corroborate the current subgroupings. This has similarly been done in a schizophrenic cohort (Sui, 2010).

CONCLUSION

- Though the overall TBI group results indicate that there are no differences between the TBI group and the controls it is possible to find groups of coherent subjects which exhibit significant differences.
- Since common clinical measures of TBI are frequently subjective, loosely defined, and/or incomplete, functional brain scanning may be a valuable tool for classification of TBI patients.

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The associations of sleep disturbances and neuroimaging findings among military patients diagnosed with mild TBI

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Abstract

Sleep disorders and poor quality of sleep are two of the most widely observed symptoms in patients diagnosed with mild TBI/PTSD that often affect recovery and rehabilitation efforts. PSG, EEG, and actigraphy, have been used to estimate objective measurements of sleep disturbances. However, despite the frequency of post-traumatic sleep–wake disturbances (SWD) such as insomnia, hypersomnia, and excessive daytime sleepiness (EDS), associations between sleep patterns and structural images of patients diagnosed with mTBI have not been studied.

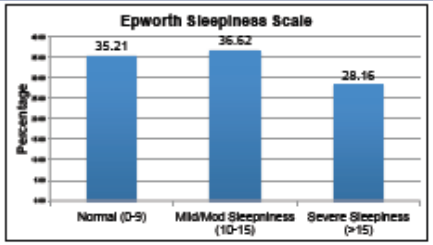
Mild TBI Population

- A retrospective study was performed in a cohort of active military personnel with mTBI/PTSD that had a neuroimaging scan and neuropsychological evaluations within two weeks from the time of in-lab PSG study.
- A total of 85 patients (age 32.47 ± 8.60, BMI 27.77 ± 5.64, 96.59% males) were analyzed.
- The analysis of the Neurobehavioral Symptom Inventory (NSI) shows that 63.51% of the patients suffered from severe to very severe difficulty with falling or staying asleep.

Symptom	% Mod – Very Severe	% Severe – Very Severe
Forgetfulness	94.52	82.19
Poor concentration	87.67	65.75
Irritability	89.19	64.86
Slowed thinking	87.84	64.86
Headaches	91.89	58.11
Poor frustration tolerance	85.14	58.11
Difficulty falling or staying asleep	78.38	63.51
Fatigue / loss of energy	81.08	52.70
Difficulty making decisions	79.45	53.42
Feeling anxious or tense	79.45	58.90

Table 1: Top ten symptoms presented by our population. 63.51% of subjects have severe sleep disorders.

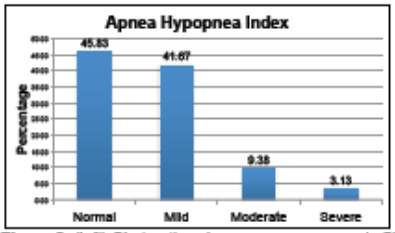
Sleep and Imaging Findings



Sleep Architecture	
Stage	% TST
N1	4.65% ± 4.1
N2	60.31% ± 11.3
N3	18.02% ± 9.5
REM	17.04% ± 9.7

Figure 1: (left) The Epworth Sleepiness Scale (ESS) shows that 65% of the mTBI/PTSD subjects presented with an abnormal amount of sleepiness. (right) Sleep architecture for the individuals under consideration.

- Other severe to very severe symptoms relevant to our study were headaches (58.11%), anxiety (58.90%), and depression (48.64%).
- The PTSD Checklist (PCLm) questionnaire shows that 60% of our patients screen positive for PTSD.
- The Epworth Sleepiness Scale (ESS) shows an average score of 11.82 ± 5.35 with 35.21% normal, 36.62% (mild-mod), and 28.16% showing severe sleepiness.
- From the PSG test it was found that patients had a sleep efficiency (SE) of 87.21% ± 10.86, arousal index of 24.25 ± 12.75, and apnea-hypopnea index (AHI) of 7.32 ± 7.74.
- Obstructive sleep apnea was seen in 55% of patients (AHI ≥5).
- From the brain MRI imaging (3 Tesla, T2 Flair) results it was found that 48.75% of the patients demonstrated punctate T2 hyperintensity lesions.
- Of the patients with T2 lesions, at a 95% confidence mean, 2.04 T2 hyperintense lesions per individual were found.



Respiratory Disturbance Index	
Normal	11.34%
Mild	26.80%
Moderate	40.21%
Severe	21.65%

Figure 2: (left) Obstructive sleep apnea was seen in 55% of patients. (right) RDI was elevated for 88% of the subjects.

Results

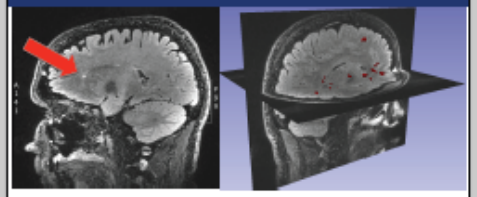


Figure 3: Punctate T2 hyperintense lesions were found within 48.75% of the individuals.

- Patients that reported having severe to very severe problems falling asleep tended to have a statistically significant higher chance of showing punctateT2 hyperintensity lesions within their MRI images ($t(69) = -2.19$, $p < 0.03$) than those with mild-moderate severity.
- Among the patients with T2 hyperintense lesions a weak but significant correlation was found between the number of T2 hyperintense lesions and the Sleep Efficiency ($R=-0.259$, $p<0.020$).
- Other PSG sleep architecture variables and AHI were not associated with T2 hyperintensities.
- A weak but significant correlation was found between PTSD (as captured by PCLm) and Apnea hypopnea index ($R=-0.241$, $p=0.043$).
- The arousal index was found to be significantly associated with anxiety ($R=0.379$, $p < 0.001$) and individuals with severe and very severe depression seem to have a tendency of having longer REM latency ($R=0.264$, $p< 0.23$) than the other group.

Conclusion

mTBI is associated with a high prevalence of subjective sleep complaints and of obstructive sleep apnea. In this cohort of military patients T2 hyperintensities were associated with subjective sleep complaints but not with most objective PSG sleep measures.

Localization of Delta Slow Wave Activity in Mild Traumatic Brain Injury (mTBI) using Independent Component Analysis

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Introduction

Localizing the origin of delta slow wave activity (DSWA) recorded with MEG/EEG has been proposed as a non-invasive method to identify grey matter abnormalities due to white matter axonal injuries. We introduce a novel approach using Independent Component Analysis (ICA) to localize multi-focal sources of DSWA in patients with mTBI.

Methods

Resting-state Magnetoencephalography (MEG) and Electroencephalography (EEG) data were simultaneously recorded using the Elekta VectorView™ whole-head MEG system with 306 channels and a 60-channel EEG montage. The 5-minute recording was acquired with 1kHz sampling rate while the patient was resting with eyes closed. Data were bandpass filtered between 0.75 Hz and 40 Hz and down sampled to 200 Hz. An ICA Infomax algorithm available in EEGLAB was used to segregate the activity of the underlying EEG/MEG generators as separate independent components (ICs), representing distinct spatial field patterns arising from either one focal cortical location or a network of multiple sources. ICs corresponding to cardiac and eye movement interferences were removed. A spectro-temporal analysis using the Short-Time Fourier Transform was used to identify the presence of DSWA on the remaining ICs. The brain generators associated to each IC showing DSWA were estimated using sLORETA available in Brainstorm.

Results

The patient was a 42-year old right-handed active duty male service member with no current use of medication and deployment history to Afghanistan and Iraq. The patient reported multiple blast and impact-related injuries, and met Department of Defense criteria for concussion. Results from T2-weighted MRI showed four white matter hyperintensities in the right frontal lobe, including one in the pericallosal region, and five white matter hyperintensities in the left frontal lobe.

Both MEG and EEG analyses revealed the presence of DSWA. Figure 1 shows a 10-second representative epoch of DSWA in an awake patient. This temporal segment with high DSWA was identified on the spectro-temporal map of IC #1.

DSWA was also identified on the spectro-temporal maps from several other ICs. The DSWA localized to multiple brain regions, as shown in figure 2. For IC #1, which accounts for 12.5% of the MEG data variance, the DSWA localized to the right superior frontal gyrus and pre-central gyrus. For IC #2 (accounting for 10.4% data variance), the DSWA localized bilaterally to the middle frontal gyrus. For IC #3 (accounting for 7.2% data variance), the DSWA localized to the left superior frontal gyrus.

Conclusions

DSWA can be identified using electrophysiological techniques. For this patient, the DSWA analyses using MEG/EEG were correlated with anatomical findings on T2-weighted MRI. These findings are consistent with previous studies examining DSWA, and therefore may in the future serve as an objective independent biomarker of TBI.

The traditional MEG source reconstruction is challenged when multiple brain generators are simultaneously active, which is particularly relevant to the analysis of resting-state brain activity. ICA can segregate the contribution of these generators into separate ICs with distinct field topographies. This approach can improve the accuracy of the source reconstruction for multi-focal sources of DSWA.

Acknowledgements

We wish to thank Kathy Meech for assisting with data collection, LCDR Karen Livornese for assisting with patient recruitment, and Joanna Vivalda for assistance with regulatory matters.

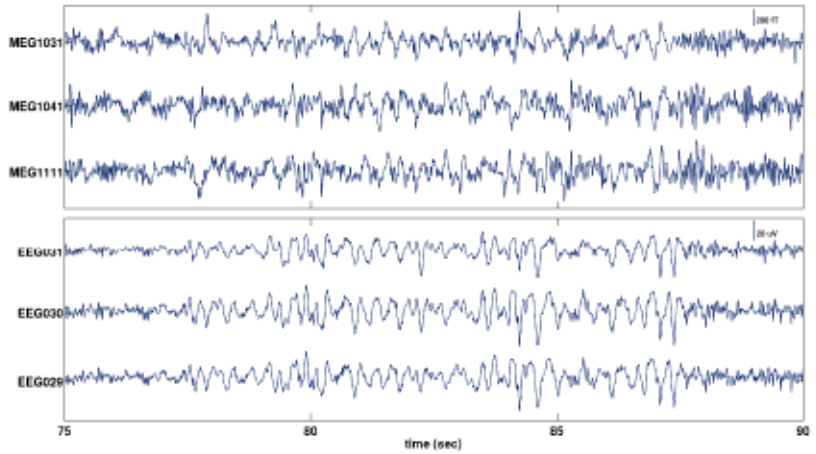


Fig 1. Raw MEG (upper panel) and EEG (lower panel) data after artifact removal using ICA. Three MEG and three EEG channels are shown on a temporal segment with DSWA.

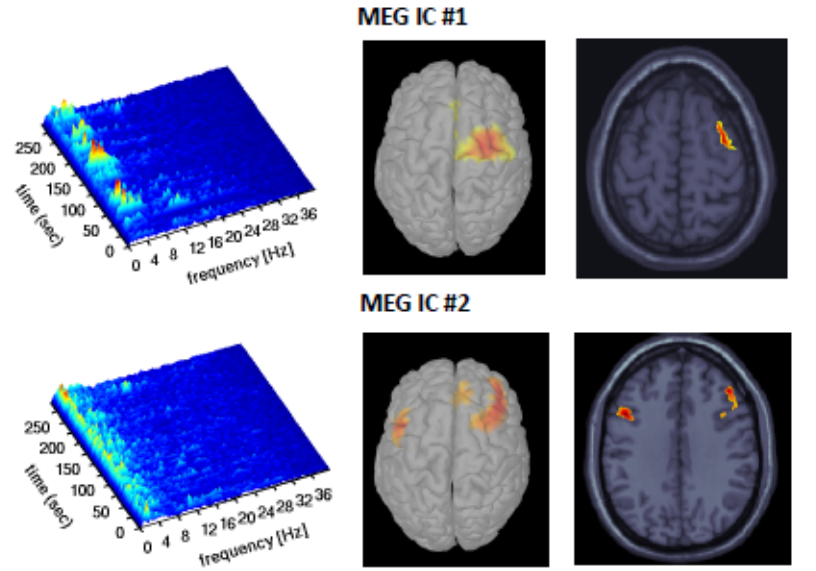
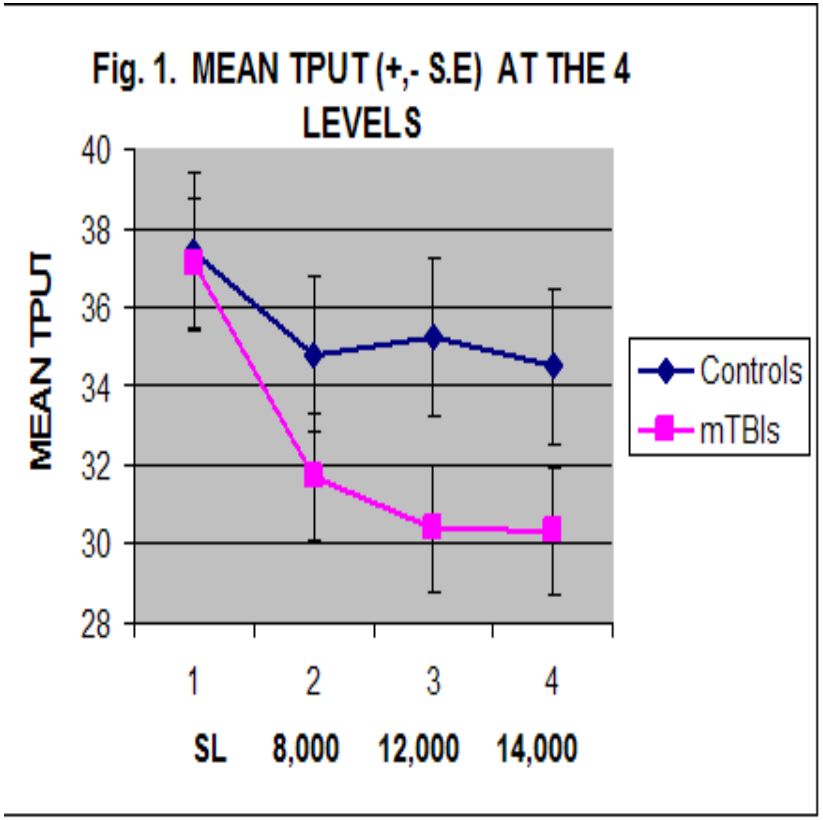


Fig 2. Spectro-temporal maps (left panels) and the corresponding source localization (middle and right panels) are shown for the first two ICs.

ANAM Matching to Sample (M2S; Memory Subtest)



- The performance decrements of mTBI (N=36) was over twice as great as the control (N=36). Note that at altitudes of 12,000 and 14,000, there is no overlap between the standard errors of the 2 groups.