Mild Traumatic Brain Injury Diagnosis:

A Consensus of Mild TBI Consensus?

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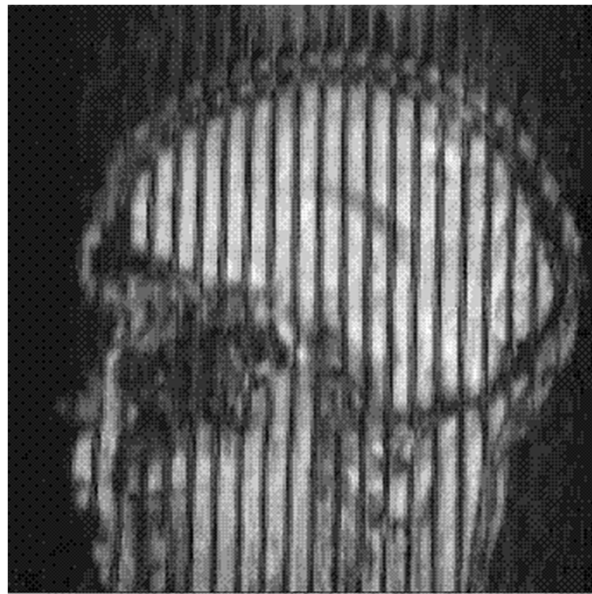University of Washington School of Medicine

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Traumatic Brain Injury:
Definition, Incidence, and Classification

Traumatic Brain Injury (TBI) defined

- A blow or jolt to the head or a penetrating injury that disrupts the function of the brain

- Clinical Classifications:
    - Mild, Moderate, Severe

- Injury Classifications
   - Penetrating (pTBI), Closed-head (cTBI)

Incidence of TBI and 'Mild' TBI Specifically

- Traumatic brain injury (TBI) affects roughly 3.5 million individuals annually in the United States

- Approximately 75% are due to 'mild' or concussive events.

- In the US military, it is estimated that roughly 20% of the deployed force suffered a head injury in the wars in Iraq and Afghanistan

- Approximately 83.3% of whom endured a mild, uncomplicated TBI or concussion.

- 1.1 and 1.9 million SRRCs occur annually in US children aged ≤18 years

- Annual costs all TBI in the United States of both direct medical and indirect lost wages are estimated to be around $60 billion with ~45% due to Mild TBI

- So…. In 5 years, another estimated 17-20 million cases or conservatively another 13 million new Mild TBI patients

- Don't forget the survivors – That's who you will likely treat (acute & long term)

Coronado et al, JSR 2012; CDC Mild TBI Report 2012; Taniellian, et al Rand Corp 2008, DVBIC: DoD Numbers for Mild TBI 2013; Bryan et al, Pediatrics 2016; Finkelstein et al, Incidence and Economic Burden of Injuries in the US 2006

Mechanisms of Injury – All TBI

Percent Distributions of TBI-related Emergency Department Visits by Age Group and Injury Mechanism — United States, 2006–2010

CDC National Hospital Ambulatory Medical Care
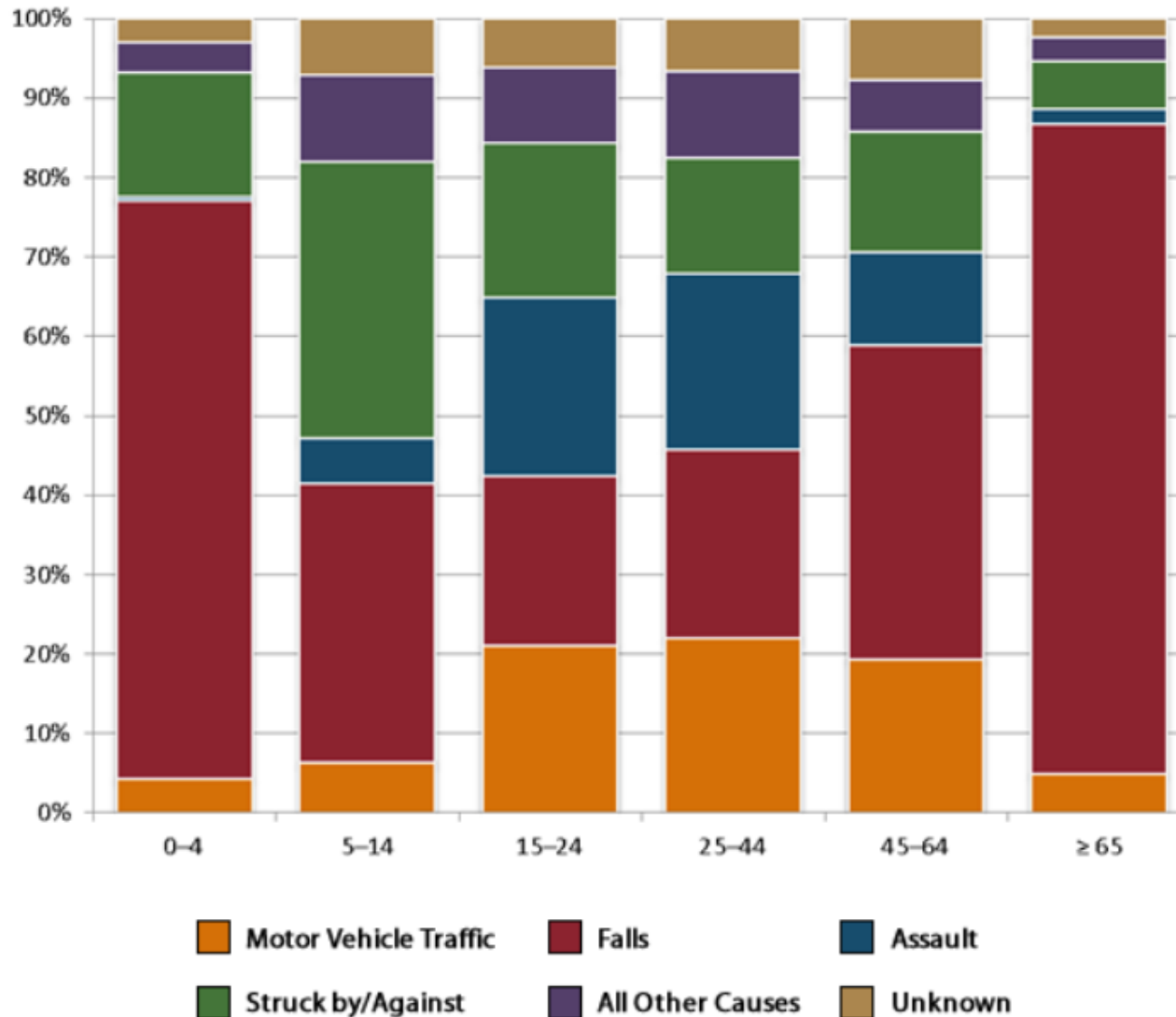
Common Mechanisms of Mild TBI

- ## In Adults:
  - 35.2% - Falls
  - 17.3% - Motor Vehicle Accidents
  - 16.5% - Being struck by an object
  - 10% - Assault
  - 20% - Other Mechanisms

- ## In Pediatrics
  - Sports and Recreational Play account for vast majority of mild TBI cases

Faul et al, TBI in ED Visits, CDC, 2010

A Quick Note on Age and TBI

- Mild TBI, like all TBI has a bimodal distribution of Age
  - Peak 1 – 15-24 years
  - Peak 2 – 65 years and older

- Recently, it was reported that 'Geriatric TBI' is the fastest growing subgroup of the brain injury population

- Persons 75 years and older have the highest rates of TBI hospitalization and death.

- Guidelines for clinical management for TBI patients 65 and older remain hotly debated and poorly understudied.
  - Something as basic as ICP or CPP management can be quite different in older patients who are more likely to be on anticoagulants, present with comorbid health conditions more prevalent in older adults (diabetes, hypertension, etc)

CDC TBI Statistics, 2010; Thompson et al, J Am Geriatr Soc, 2008

Really more of a Spectrum

Severe   Moderate   Mild   Concussion

Table 1. TBI grading scale based on neurological symptoms

TBI Level➔	Mild	Moderate	Severe	{Penetrating}
GCS	13-15	9-12	3-8	(any)
AoC	</= 24 hrs	>24 hrs	>24 hrs	(any)
LoC	0-30 min	31 min-24 hrs	>/=24 hrs	(any)
PTA	</=24 hrs	24H - 7 days	>/=7 days	(any)

GCS, Glasgow Coma Scale; AoC, period of altered consciousness; LOC, period of loss of consciousness; PTA, duration of post-traumatic amnesia.

Benzinger et al., Journal of Neurotrauma *2008*

Misnomer - Concussion <u>vs</u> TBI
Concussion == TBI

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Concussion Grades

Concussion Grade	Consciousness	Signs & Symptoms	Headache
1 MILD	No Loss of Consciousness	Post-Concussion symptoms for less than 24 hours. Post-traumatic amnesia for less than 30 min.	Probable (10 minutes-1 day)
2 MODERATE	Loss of Consciousness < 1 min	Post-Concussion symptoms for more than 24 hours, but less than 7 days. Post-traumatic amnesia for more than 30 min, but less than 24 hours.	Probable (24 hours-7 days)
3 SEVERE	Loss of Consciousness > 1 min	Post-concussion symptoms for more than 7 days. Post-traumatic amnesia for more than 24 hours.	Likely (Greater than 7 days)

(although not widely adopted and of unclear clinical significance)

And the Concept of Concussion is Not New….

Al-Razi
Abūbakr Mohammad-e Zakariyyā-ye Rāzī
ابوبکر محمد زکریای رازی

- First account of concussion is documented from the great Persian Physician Rhazes in 900 AD

- Translations of his work describe his observation in patients following head impacts of:

- "Abnormal transient physiological state <u>without</u> gross brain lesions or head wounds"

And for 1000+ years the concept evolved driven mostly by advancements in medicine (example: The Microscope!)

Table *Historical development of concussion*

Author	Year	Term	Description	Effects
Rhazes	900	Commotio cerebri	Abnormal transient physiologic state without gross brain lesions	Transient
Avicenna	1020	Commotio cerebri	As per Rhazes definition	Transient
Lanfrancus	1280	Commotio cerebri	Distinguished commotio (shaking) with no damage from contusio cerebri with structural damage	Transient
du Chauliac	1363	Commotio cerebri	Injury to the head without wounding of the brain or break of the skull	Transient
Brunshwig	1497	Commotio cerebri	Mild brain injury distinguished from penetrating brain injury	Transient
de Carpi	1518	Commotio cerebri	Defined as brain injury without fracture or hemorrhage	Transient
Coitier	1573	Commotio cerebri	Brain commotion causing impairment in memory, understanding, and judgement	Transient
Fabricius	1578	Commotio cerebri	Blow causing lethargy and vertigo	Transient
Pare	1579	Embranlement*	Blow to the head causing symptoms	Variable
Queyrat	1657	Commotio cerebri	Injury due to the "ebb and flow" of nervous tissue within the brain	Transient
Marchetti	1665	Concussion	"Alienation of the mind with privation of senses"	Transient

* Although Ambroise Pare reputedly spoke no Latin, his term *embranlement* may be translated as *to shake* in old French. When his books were translated into Latin, the terms *commotio cerebri* and *concussion* were variably used in place of *embranlement*. The term *concussion* is probably derived from the Latin verb *concutere* (to shake).

McCrory, P.R. and Berkovic, S.F., Neurology 2001

Mild Traumatic Brain Injury and Concussion in the 21st Century

Consensus around Mild TBI Consensus?

Definitions of mild TBI

Organization	Loss of consciousness	Post-traumatic amnesia	Glascow Coma Scale	Focal neurologic deficits	Other
American College of Rehabilitation Medicine	±, lasting 0–30 min	<24 h	13–15 after 30 min	±, may be transient	Alteration of mental state (e.g., confusion, disorientation)
Centers for Disease Control	±, lasting 0–30 min	Not required		±	Headache, dizziness, fatigue
World Health Organization	±, lasting 0–30 min	<24 h	13–15 at presentation	±	
Department of Veterans Affairs	±, lasting 0–30 min	<24 h	Best score 13–15 in first 24 h	±	Alteration of consciousness <24 h, normal structural imaging

Very on PTA guidelines
Very on GCS guidelines
Very on specific Symptoms
Very on Radiographic Findings requirement

Is there a 'right' way to define?

Caveats to 'Strict Criteria' for Mild TBI

- Much is based on subjective recall by patient

- Even main AoC definition is subjective
  - "experience of feeling dazed or disoriented and/or being unable to account for duration of time after the injury"

- AoC can be impacted by 'non-TBI' elements
  - Intoxication
  - 'Adrenaline rush'
  - Significant psychological trauma surrounding the event

- A broad range of severity is considered
  - Is 30 seconds of LOC really the same thing as 30 minutes?....
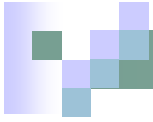 - Is 5 minutes of PTA really the same thing as 5 hours? 15 hours? 24 hours?

More Recent Mild TBI Subdivisions

- Complicated Mild TBI
  - Driven by imaging findings most often on CT
  - Studies suggest pathoanatomic lesion findings negatively impact outcome

- Uncomplicated Mild TBI
  - Unremarkable imaging (most often a negative head CT)
  - Often used interchangeably with 'Concussion' per Mild TBI definitions that note 'lack of radiological findings' in criteria but again this is not universal

Williams et al, Neurosurg 1990; Iverson et al, Brain Inj 2006; Kashluba et al, Arch PMR 2008; Yuh et al, Annals of Neurology 2013

Discussion on Concussion

- More recently Concussion has been defined as: "complex pathophysiological process affecting the brain induced by traumatic biomechanical force"

- Primarily driven by Sports and Rec Concussion Consensus Conferences

- Like overall TBI Dx – Thresholds are arbitrary – Does 60sec LOC matter?

Not much has changed since the 1600s when concussion was described as:
*A singing in the ears after the wound is received.
*Falling after the blow
*Swooning for a time
*Dazzling of the eyes
*Slumbering after the wound is received
*Giddiness which passes rapidly

- □ Crucial to obtain a clear history and exam at time of evaluation.

- □ NO single test to date can definitively diagnose a Concussion

- □ Of Note – Efforts to understand sensitivity and specificity of a variety of common concussion screening metrics found that in particular cognitive assessments were quite poor in tracking Dx and recovery.

McCrory et al J Athletic Trainers 2009; Harmon et al Clin J Sport Med 2013; Giza et al, Neurology 2013; Katz et al, Handbook of Clin Neurology, 2015; Register-Mihalik et al, JHTR 2013; Reed, A. Chirurgorum comes. 1667

Mild Traumatic Brain Injury: Screening and Diagnosis

Challenges for Clinicians:
How confident of Dx for Mild TBI?

- LOC/AOC/PTA is based on patient self report

- Cultural, language, demographic differences such as age/gender can all influence response to history intake

- Collateral source information may be sparse

- Psychological trauma of the event may impact patient endorsement

- Concomitant considerations of patient presentation
  - Alcohol
  - Sedative drugs
  - Other centrally acting Rx
  - Or does everyone really come into the ED squeaky clean?....

- It should not be overlooked that Clinician bias can impact this determination

- In a recent study of practitioners who identified as treating mild TBI of the 1000+ respondents, only 55.3% identified the standard patient case video as mild TBI Dx
  - The scenario was an adolescent and mother who report symptoms the adolescent was experiencing at the time of the examination to include irritability, photophobia and fatigue. In addition, they described headache and nausea that occurred immediately following the injury 3 days prior.

Graves et al, JAANP 2016

Use of Neuroimaging Diagnostics

- Most common first line of defense for imaging diagnostics is a Head CT

- While helpful with moderate to severe TBI to guide acute management and decision making about neurosurgical intervention – Radiographic findings are often sparse or absent in Mild TBI.

- So you have an impaired patient, with a negative head CT, and questionable history – Is it Mild TBI?

- Are other imaging techniques more sensitive to pathoanatomic lesion formation following mild brain injury?

- Question: How confident should we be in a 'clean head CT' means 'clean bill of brain health'?

CT vs. MRI Comparison from TRACK-TBI

Pratik Mukherjee,
MD PhD
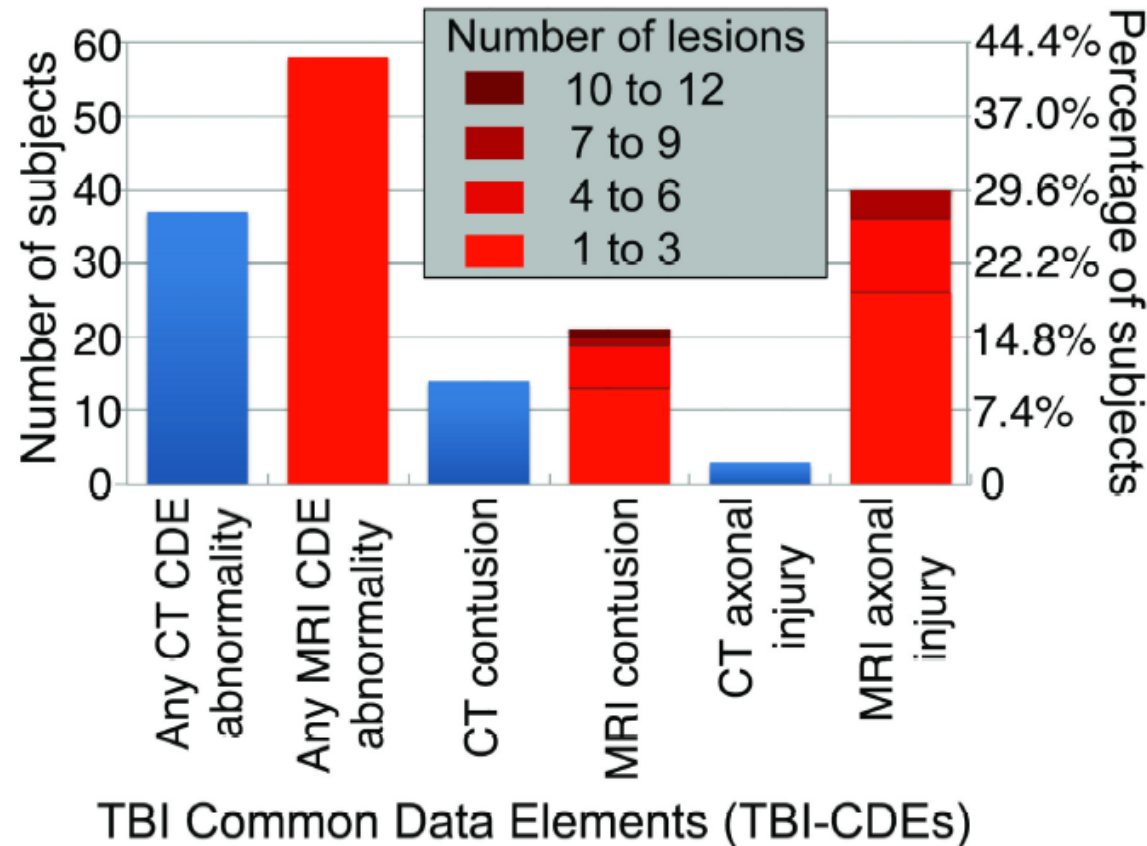
Esther Yuh,
MD PhD

- CT is the most common radiographic modality in used in Emergency Departments.
- MRI consistently identifies greater pathoanatomic lesion load than CT
- ***28% of patients*** with ***normal*** CT had ***abnormal*** MRI lesions consistent with brain injury.
- Most common pathoanatomic lesions in mild TBI – multifocal microhemorrhage (TAI/DAI), contusion, extra axial hematoma

Yuh et al, Annals of Neurology, 2013

Common Mild TBI Symptoms
What's Not Included…. Is it really Mild TBI Specific?

Difficulty thinking clearly	Headache Fuzzy or blurry vision	Irritability	Sleeping more than usual
Feeling slowed down	Nausea or vomiting (early on) Dizziness	Sadness	Sleep less than usual
Difficulty concentrating	Sensitivity to noise or light Balance problems	More emotional	Trouble falling asleep
Difficulty remembering new information	Feeling tired, having no energy	Nervousness or anxiety	

Headaches...
Feelings of Dizziness ....
Nausea and/or Vomiting ....
Noise Sensitivity,
      easily upset by loud noise ....
Sleep Disturbance...
Fatigue, tiring more easily ....
Being Irritable, easily angered ....
Feeling Depressed or Tearful.....................
Feeling Frustrated or Impatient ....

Forgetfulness, poor memory ....
Poor Concentration ....
Taking Longer to Think ....
Blurred Vision ....
Light Sensitivity,
      Easily upset by bright light................
Double Vision ....
Restlessness ....

Who in this room wouldn't endorse something on these lists? Do we all have Mild TBI?

King et al, Neurology 1995; CDC Mild TBI/Concussion 2017

Some Attempt at Symptom Categorization

- It has been suggested that consideration of symptoms into 3 general domains may be clinically useful.

- These Include

- Somatic – e.g. headache, nausea, dizziness, photophobia, phonophobia, sleep disturbance

- Cognitive – e.g. concentration, memory or executive dysfunction

- Emotional – e.g. irritability, depression, anxiety, mood lability, even adjustment disorder

- Although emphasis should be given on the 'combination' of 'recent transient impairment in neurological function' and a some or all of the above.

McCrory et al J Athletic Trainers 2009; Katz et al, Handbook of Clin Neurology, 2015

Somatic Symptoms after Mild TBI

- Headache
    - Most commonly reported somatic and some would say commonly reported symptom (period) following Mild TBI
    - Studies report up to 90% of patients have PTH
    - 47-78% of patients have PTH 3-6 months post-injury
    - HA Type: tension-type followed by migraine are most common followed by cervicogenic and craniomandibular often arising from extracranial injuries.
- Dizziness
    - Central: DAI & 2nd pathology found to disrupt central vestibular pathways w or w/o hearing loss
    - Peripheral: positional vertigo caused by otolith displacement, labyrinthine concussion caused by inner ear tissue disruption, in addition to cervical injury caused by upper cervical spine trauma disrupting connections to visual and vestibular systems known as 'cervical vertigo' and P-T migraine
- Sleep Disturbance/Fatigue
    - Prior work in civilians found ~22% of Mild TBI patients had sleep disturbance 3-6 months post injury
    - More recent efforts in Combat-related Mild TBI found 52-48% had moderate to severe sleep disturbance 1 year and 5 years post-injury (likely complicated by comorbid mental health conditions)

Faux etal, Pain Med 2008; Levin et al, J NeuroSurg 1987; Lew et al; Am J Phys Med Rehab, 2006; Horn et al Brain Inj Med, 2013; Maitland etal, Curr Neuro Neurosci 2001, Leddy et at; Sports Health 2012; Mac Donald et al JNTA 2017; Mac Donald et al JAMA Neuro; 2017

Cognitive Symptoms after Mild TBI

- Cognitive Symptoms most often normalize in the subacute period post injury

- Prior work suggests:
  - ☐ Few patients exhibit cognitive symptoms after 1-2 weeks and very few after 1-3 months post injury
  - ☐ 4 different meta-analysis studies looking at relationship between cognitive symptoms and time post-injury found no significant impact after 3 months
  - ☐ In sports concussion resolution of cognitive symptoms was reported to occur by 1 week in the majority of athletes.

- Acute screening 'yes', Subacute/Chronic 'no?'

Katz etal, Hand.Clin Neuro,2015; Yang etal, JTrauma,2007; Ruff etal, Neurorehab,2011; McCrea etal, JAMA2003

Emotional Symptoms after Mild TBI

- Depression
    - Rates of 11-44% of depression in civilians following Mild TBI
    - Rates of 39-50% of moderate to severe depression following combat-related Mild TBI
    - Preinjury psych disorders can contribute to post-injury depression
- Post-Traumatic Stress
    - Rates have been recently reported to be around 30% in civilians following Mild TBI and 25-60% in combat-related Mild TBI meeting moderate to severe criteria.
- A Note on Adjustment Disorder
    - Beginning to be appreciated as a significant condition following injury which should not be overlooked and could lead to much more severe depression, PTS, anxiety, irritability, among others in particular in previous high functioning patients & competitive athletes

- Challenge: Considerable overlap in symptoms post-TBI and those with Psych Symptoms in the absence of TBI – Studies have reported as high as 86% overlap – So…. Are you treating the TBI or treating a preexisting condition?..... Does it matter to the patient?.....

- Worth also noting that pre-existing Psych conditions often appear exacerbated following exposure and certain conditions are thought to have higher incidence of TBI exposures (Bipolar, Schizophrenia, etc)

Kreutzer etal Brain Inj 2001; Iverson etal TBI Principles & Practice 2013; Manley etal TRACK-TBI 2017; Mac Donald etal, JNTA 2017; Bombardier etal, JAMA 2010

From Symptoms to Syndrome

- PostConcussive Syndrome (PCS) / PostConcussive Disorder (PCD)
- ICD-10 Criteria for PCS
  - Syndrome following head trauma
  - At least three of the following symptoms present: HA, Dizziness, Fatigue, Irritability, Difficulty concentrating, Memory impairment, Insomnia, Intolerance to stress, emotion, or alcohol.
- PCD defined by DSM-IV adds:
  - Must include concentration or memory impairment
  - Impact of all symptoms significantly impact social or occupational functioning
  - Present for at least 3 months
- As noted before – much of the above can also occur for non-brain injury conditions making the determination sometimes feel ambiguous.
- And prior work by the WHO found 'no empirical support for the ICD-10 or DSM-IV being specific for Mild TBI.

McCauley et al, J Clinical Exp Neurospych, 2008; Carrol et al, J Rehab Med, 2004

Risk Factors for Poor Outcome

- TBI in particular Mild TBI/Concussion has been reported to be 'rarely sufficient' to explain long-term symptoms.

- 'What you bring to the injury vs. what the Injury brings to you (mod/sev)'

- Risk Factors acting in combination with Injury Exposure
    - Older Age
    - Pre-existing mental health conditions
    - Personality Factors – interestingly a study of emotional risk factors for poor Mild TBI outcome found ~50% met criteria for Axis II personality disorders with histrionic, narcissistic, and compulsive traits being highest on the list
    - Preinjury life stressors – homelessness, abusive home environment, even ongoing separation/divorce, lack of good social support
    - Mild TBI with Radiographic Findings: 'Complicated' Mild in particular with those that have 4 or more mutifocal microhemorrhage, 1 or more contusions, depressed skull fractures
    - Genetics – currently APOE most studied as a G X E risk
    - And Litigation should not be overlooked…. Studies have shown that patients in ongoing litigation often endorse symptom prolongation at much higher rates that those who are not.

Meares etal, Neuropsych, 2011; Lange etal, JHTR 2011; van Veldhoven etal, JNNP 2011; Evered etal, Assessment 2003; Yuh etal, Annals Neuro, 2013; Carroll etal, J Rehab Med 2004; Belanger etal, J Int Neuropsych Soc 2005

Impact of Bias – Trying to find Balance

- Worth noting that Outcome can also be influenced by Perception

- Concept of 'expectation as etiology' describes patients attributing pre-existing symptoms to the brain injury.

- Rebranded in 2010 as 'Good old days' bias where the patient's perceive themselves as healthier or higher functioning before the injury than they actually were – This misperception can impact recovery

- Even Health Care professionals can exacerbate this by focusing on potential for debilitating conditions or permanent brain damage
  - Caution on 'Iatrogenic Impact' of Patient Communication

- The flip side – If the Clinician minimizes too much it can cause patients to question their conditions when they may truly have symptoms arising from the injury

- The Goal – Baby Bear's Porridge!

Mittenberg et al, JNNP 1992; Iverson et al, Clin Neuropsych 2010, Wood et al Brain Inj 2004

Mild Traumatic Brain Injury: Evaluation

With so Many Caveats – Where to Start?!

- Accurate Diagnosis & Differential Diagnosis
  - Mild TBI diagnosis – great – what about:
  - Associated Injuries
  - Comorbidities
  - Premorbid Conditions
  - Postinjury biological factors
  - Postinjury psychosocial factors
  - Complete (as possible) accounting of symptoms

- For Diagnosis – as detailed account as possible from the patient and witness/collateral source if available of the events surrounding the injury – review of neuroimaging (CT/MRI) but with understanding of the strengths and limitations of each modality

- Differential Diagnosis – consider history for previous injuries, prior neurologic or psychiatric problems (not necessarily Dx but behavioral indicators of underlying conditions), substance abuse, learning disabilities, concomitant injuries, collection from collateral source if available to corroborate information and fill in details.

Katz et al, Handbook of Clin Neurology, 2015

Additional Assessment Elements

- Evaluation of patient personality traits, coping style

- Neurologic exam should include screening for
  - Headache
  - Dizziness
  - Mental Health comorbidities

- General counsel and education to manage post-injury expectations 'just right' can help
  - General information about common symptoms, recovery timeline, where to go for follow up care if symptoms don't resolve in ~1-2 weeks.
  - Most guidelines also suggest
  - AVOID: driving, dietary stimulants like caffeine, making major taxing decisions or physical fitness until symptoms resolve
  - ENCOURAGE: good sleep hygiene, good nutrition, pacing return to demanding work or physical activities
  - A note on Cognitive Rest – Became popular without good evidence-based support for approach and more recent efforts have shown it can be <u>detrimental</u> to recovery
  - More recently – consideration of light activity up to symptom recurrence has been prevailing recommendation – e.g. walking, stretching, light yoga, etc – may also help soreness from musculoskeletal injuries sustained at the time of Mild TBI

Katz et al, Handbook of Clin Neurology, 2015; McCrory et al, J Sport Med 2005; de Kruijk et al, JNNP 2002, Leddy et al, Sports Health 2012; Leddy et al JHTR 2013

Exercise is Medicine Following Mild TBI

- Recently ACSM endorsed the role of 'Exercise is Medicine'

- Goal to Encourage EIM to be
a part of standard health care

- Global initiative with Mild TBI relevance

- Benefits of Exercise following Mild TBI

  - ☐ Promotes neurocognitive recovery and symptom reduction

  - ☐ Improves depression symptoms

  - ☐ Improves recovery of Post-Concussive Symptoms with gradual training build

  - ☐ Mechanistically – early evidence suggests exercise restores autonomic function improving cerebral perfusion, autoregulation, and overall CBF

- Goal following Mild TBI is after 2-3 days of rest and recovery gradual reintegration back to physical activity focused on aerobic exercise below symptom threshold

Leddy et al, Clin J Sport Med, 2010; Baker et al, Rehab Res Pract, 2012: Leddy et al, JHTR 2013; Lojovich et al, JHTR 2010

Final Thoughts on Consensus

- No two brain injuries are a like
- Focus on treating the symptoms and other conditions more than treating the brain injury
- On the horizon we may be able to actually more directly 'treat' the brain injury (e.g. new neuroinflammation and tau/axonal stabilization drugs currently under development but this will need more selective diagnostics)
- Management of the symptoms means also management of the patient (are they a catastrophizer, are they a minimizer) and treating them in their specific environment (do they have social support, is transportation an issue for them, can they take days off work or do they have limited financial resources)
- Diagnostics currently only get us so far in appreciate underlying pathophysiological changes that may have occurred in the brain following the exposure.
- YOU the Clinician must make an informed decision as the diagnosis and treatment considerations to date remains in your hands. No pressure….
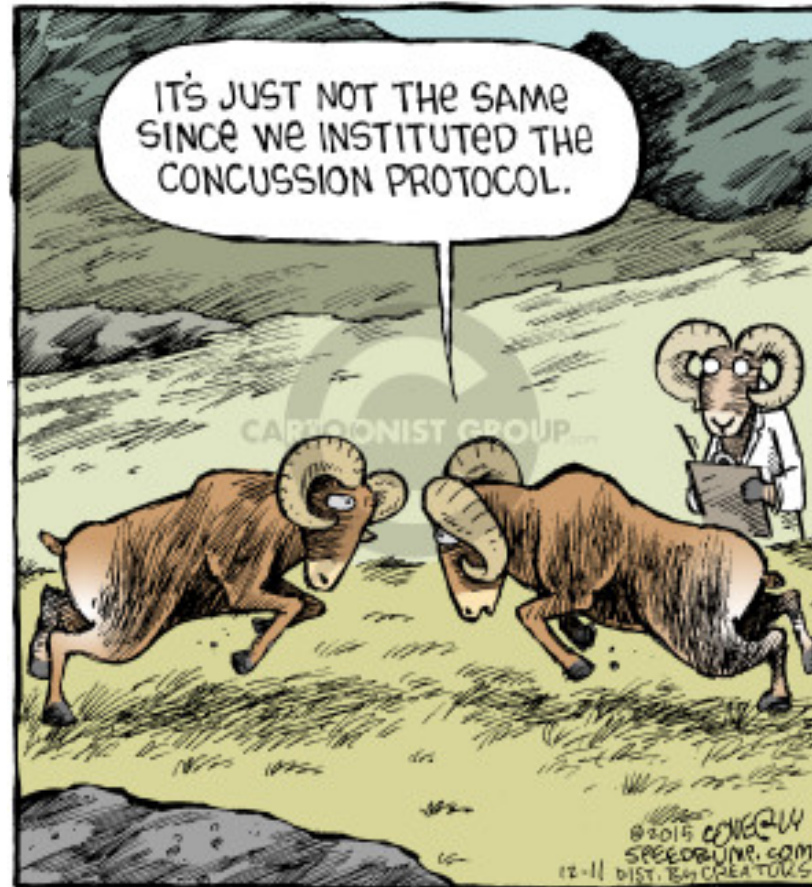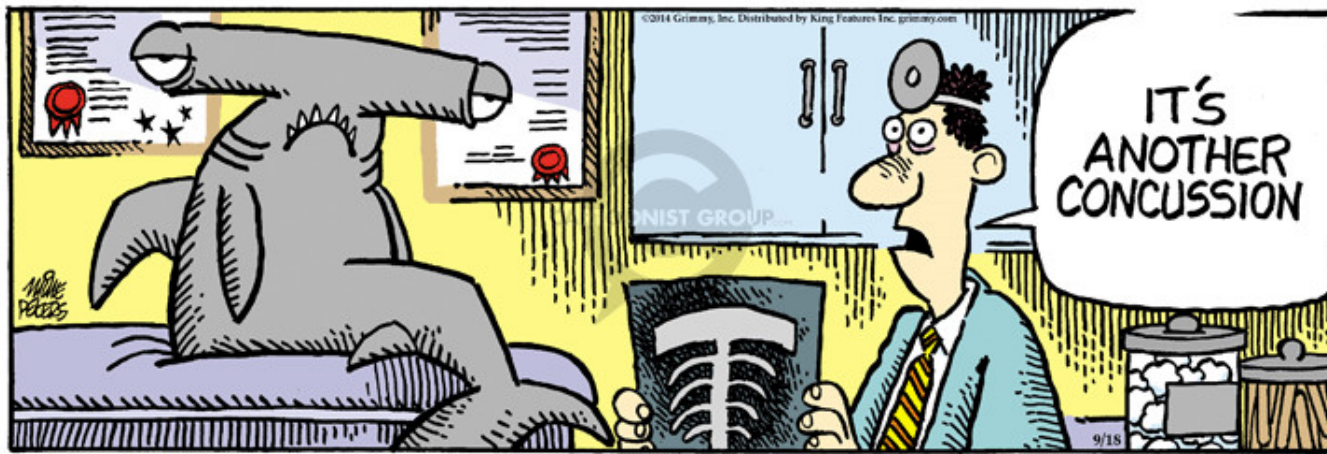
Combat-related Concussion: Understanding trajectories of long-term clinical and imaging outcome

Disclosure: No Apparent Conflicts of Interest

- Funding for this research was provided by:
  - NIH RO1 (Comp. Renewal) - <u>E</u>valuation <u>O</u>f <u>L</u>ongitudinal outcomes in mild TBI Active-Duty Military and <u>Ve</u>terans 10-Year – The EVOLVE10 Study (PI: C. Mac Donald)
  - NIH RO1 - <u>E</u>valuation <u>O</u>f <u>L</u>ongitudinal outcomes in mild TBI Active-Duty Military and <u>Ve</u>terans – The EVOLVE Study (PI: C. Mac Donald)
  - DoD - <u>E</u>valuation <u>O</u>f <u>L</u>ongitudinal outcomes in mild TBI Active-Duty Military and <u>Ve</u>terans -Brain Donation Registry Supplement (PI: C. Mac Donald)
  - DoD-CENC -<u>A</u>ssessment of long term outcome & <u>D</u>isability in <u>A</u>ctive-duty military <u>P</u>rospectively examined following concussive <u>T</u>BI: The ADAPT Study (PI: C. Mac Donald)
  - DoD - Advanced MRI in US Military Personnel with Acute Mild Traumatic Brain Injury Assessed in Kandahar (PI: D. Brody, Director: C. Mac Donald)
  - DoD - Advanced MRI in Acute Military Traumatic Brain Injury (PI: D. Brody, Director: C. Mac Donald)
  - DoD - Advanced MRI in Blast-related Traumatic Brain Injury (PI: D. Brody, Director: C. Mac Donald)

- Consultation provided to: NeuroTrauma Sciences, LLC which is independent and unrelated to the work discussed in this presentation.

Motivation for the Current Research

- Current Challenge:
  - While previous work has examined imaging and clinical outcomes in combat deployed veterans, most studies have been limited by single time point evaluations with exposure history based largely on self-report of events years prior.

- Questions remain regarding:
  - How imaging characteristics and clinical outcomes evolve or resolve over time following combat-related mild traumatic brain injury (TBI) and/or concussion.
  - How this may impact the service member's long-term outcome.

- Potential Solution:
  - Through collaborative efforts at Landstuhl Regional Medical Center, Kandahar Airfield, Camp Leatherneck and academic universities in the United States, we have been provided the unique opportunity to follow the very same patients from the point of injury in theatre to both 1-year, 5-year, and now 10-year outcome.
  - These longitudinal studies allow for the rare occasion to evaluate progression post exposure and in many cases progression as the SM transitions from AD to Civilian/VA care following service separation.

Statistical Perspective

- **2.6**
- 20
- 33
- 1
- 0

More than 2.6 Million US service members have deployed in the recent conflicts to Iraq and Afghanistan. More than a third have completed multiple deployments.

There are more than 22 Million US service members and veterans living from all previous service and world conflicts

www.dvbic.org/tbi-numbers.aspx, Scholten 2012, Taylor 2012, Gavett 2011

Statistical Perspective

- 2.6
- **20**
- 33
- 1
- 0

~20% of the more than 2.6 million service members sustained <u>at least</u> one brain injury during deployment.

Less known from prior conflicts as the clinical definition has evolved over the decades but all reports suggest that mild TBI in particular was poorly underestimated

Warden, J Head Trauma Rehab *2006,* www.dvbic.org/tbi-numbers.aspx, Scholten 2012, Taylor 2012, Gavett 2011

Statistical Perspective

- 2.6
- 20
- **33**
- 1
- 0

One third of returning service members have been diagnosed with mental health issues particularly Post-Traumatic Stress Disorder

Harvard University Kennedy School of Government 2013 Report

Statistical Perspective

- 2.6
- 20
- 33
- **1**
- 0

The current estimated cost of providing medical care to Iraq/Afghanistan US veterans will near <u>$1 trillion</u> in the coming years and may exceed this if the number of complex cases continues to surpass estimates.

Bilmes, L.J, Institute of Public Governance & Management, 2011

Statistical Perspective

- 2.6
- 20
- 33
- 1

- **0**

*The current success rate of Brain Injury therapies translating from preclinical models to human is **ZERO** and is still zero in 2019….*

Benzinger et al., J Neurotrauma 2009

TBI Clinical Trials – Where are we now?

- A PubMed search reveals 30 TBI clinical trials since 1993, 25 of which have been in the last 15 years and 13 of which have been in the last five years.

- All 30 trials failed to find a significant effect for treatments that were supported by extensive preclinical studies and Phase I and II trials.

- Treatments Included
  - Hypothermia and temperature control (11 studies)
  - Hypertonic saline (three studies)
  - Progesterone (two studies),
  - Prostacyclin (two studies)
  - Surgical intervention (one study),
  - Intracranial pressure monitoring (one study)
  - Other pharmacological interventions (10 studies).

- The estimated total cost of these trials is $1.1 billion.

The Challenge in particular with 'mild' TBI

Which one of these patients has a brain injury?

History of Combat-Related mild TBI/Concussion & PTSD

During World War I, soldiers from the British Expeditionary Force began to report medical symptoms after combat including tinnitus, amnesia, headache, dizziness, tremor, and hypersensitivity to noise. While these symptoms resembled those that would be expected after a physical wound to the brain, many showed <u>no signs of head wounds</u>.

Today we refer to this as Mild TBI/Concussion.

THE STUDY OF SHELL SHOCK.   FEB. 13, 1915

A CONTRIBUTION TO THE STUDY OF SHELL SHOCK.

BEING AN ACCOUNT OF THREE CASES OF LOSS OF MEMORY, VISION, SMELL, AND TASTE, ADMITTED INTO THE DUCHESS OF WESTMINSTER'S WAR HOSPITAL, LE TOUQUET.

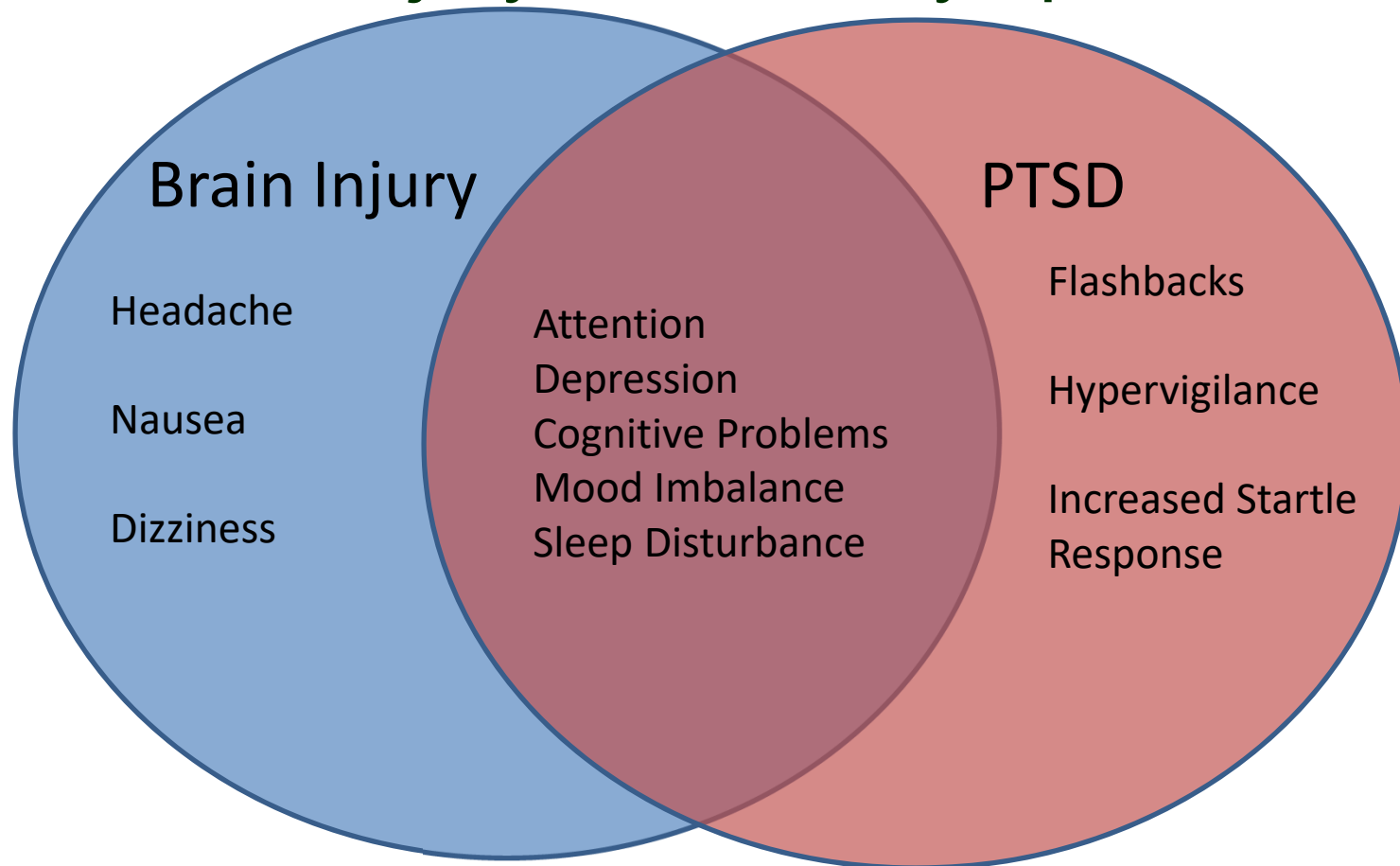BY CHARLES S. MYERS, M.D., Sc.D. CAMB., CAPTAIN, ROYAL ARMY MEDICAL CORPS.

THE remarkably close similarity of the three cases which are described in this paper is shown in the following synopsis :—

Some 60–80% of shell shock cases displayed acute neurasthenia, denoting symptoms of fatigue, anxiety, and depressive mood.

Today we refer to this as PTSD.

Attempting to Disentangle
Brain Injury & PTSD Symptoms

Brain Injury

Headache

Nausea

Dizziness

Attention
Depression
Cognitive Problems
Mood Imbalance
Sleep Disturbance

PTSD

Flashbacks

Hypervigilance

Increased Startle
Response

But this can be confounded by medications and doesn't account for other potentially co-occurring mental health conditions (e.g. depression, anxiety, adjustment disorder, etc)

Hoge, *2008;* Warden, *2006;* Benzinger et al., *2008;* Ling et al., *2009*

The Invisible Wounds of War

just because someone doesn't have scars, doesn't mean they're not battling.

But are they really invisible or have we just been using insensitive technology to visualize them?
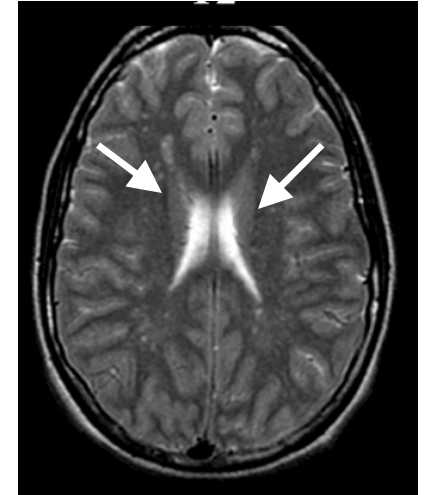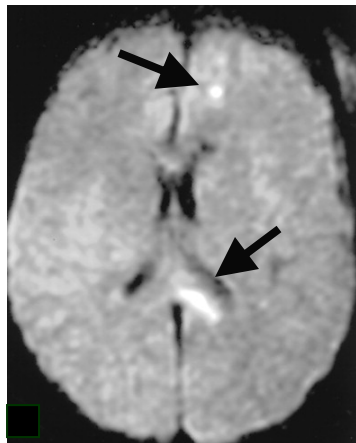
Diagnostic Imaging Applied to mild TBI

(exemplars, not an exhaustive list)

CT Image

Inverted T2* Image

- CT recognizes punctate hemorrhage *associated* with axonal injury due to shearing of blood vessels

- T2-weighted MRI recognizes edema again *associated* with axonal injury due to energy failure or breakdown of blood brain barrier

- T2*/SWI MRI recognizes small areas of hemorrhage again due to the shearing of blood vessels with much higher sensitivity than CT

- Diffusion weighted MR imaging (DWI) recognizes global movement of water in areas of ischemia *associated* with axonal injury
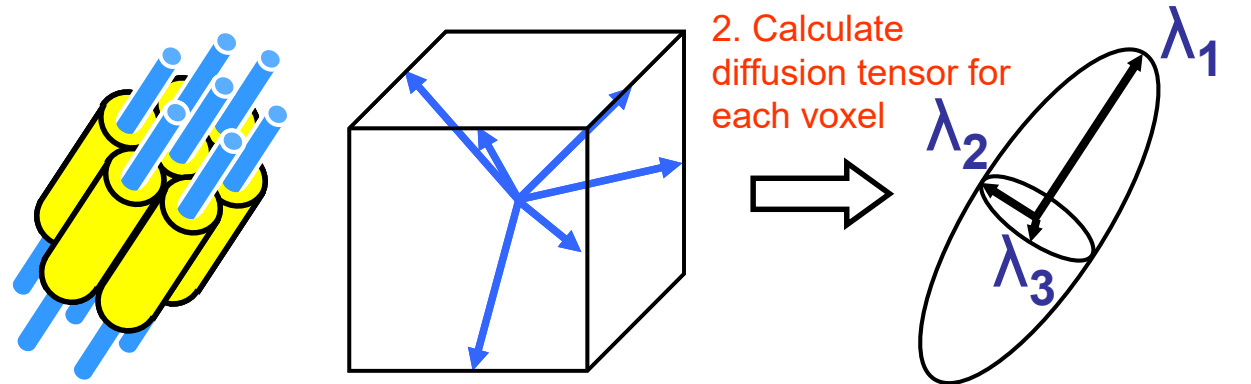
NONE OF THESE TECHNIQUES DIRECTLY ASSESS INJURED AXONS

T2 Image

DWI Image

Diffusion Tensor Imaging (DTI)

A **Diffusion Tensor Imaging**
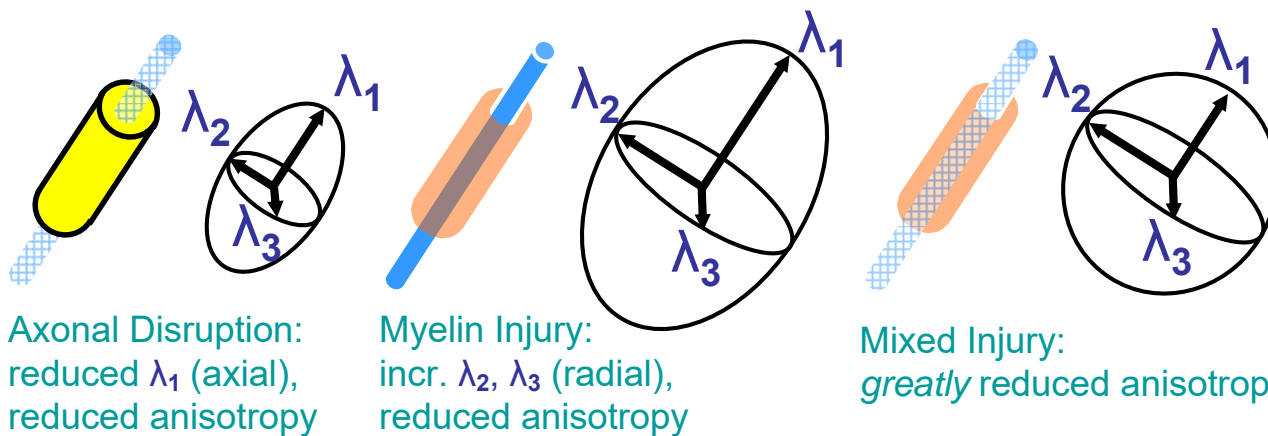
2. Calculate diffusion tensor for each voxel

λ_1

λ_2

λ_3

Brain white matter: organized, myelinated axons

1. Collect diffusion weighted images in six or more directions

3. Separate parallel (λ_1, axial) from perpendicular (λ_2, λ_3, radial) diffusion. Calculate anisotropy.

B **Traumatic axonal injury: simplified model**

λ_1 λ_2 λ_3

λ_1 λ_2 λ_3

λ_1 λ_2 λ_3

Axonal Disruption: reduced λ_1 (axial), reduced anisotropy

Myelin Injury: incr. λ_2, λ_3 (radial), reduced anisotropy

Mixed Injury: *greatly* reduced anisotropy

Figure adapted from M. Budde

Injury vs. Imaging Parameter

Injury Type	RA/FA	DWI <D>
Axonal Injury	⬇	⬇
Myelin Injury	⬇	⬆
Mixed Injury	⬇⬇	⬇⬆

$$FA = \sqrt{\frac{1}{2}} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}}{\sqrt{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

$$\langle D \rangle = \frac{(\lambda_1 + \lambda_2 + \lambda_3)}{3}$$

$$RA = \sqrt{\frac{(\lambda_1 - \langle D \rangle)^2 + (\lambda_2 - \langle D \rangle)^2 + (\lambda_3 - \langle D \rangle)^2}{\sqrt{3} \langle D \rangle}}$$

Evaluation Of mild TBI Long-term outcome in Active-Duty US Military and Veterans
The EVOLVE Study

- **Proposal Objective**: The overall goal of this study is to investigate long-term effects of mild-concussive traumatic brain injury (TBI) sustained during deployment in US military personnel using advanced MR imaging and clinical outcome measures.

- **Overarching Hypothesis:** We hypothesize that early clinical and imaging measures can be used to predict later stage clinical outcome offering important insight into the long-term impact of war-time mild TBI guiding new recommendations for clinical management and therapeutic intervention.

- These are the first studies to successfully complete prospective, observational, longitudinal combined clinical and imaging research in Active-Duty US Military in combat from the point of injury in combat to long term outcome.

Study Design

- *Study Design: Prospective, Observational, Longitudinal Research Study*
- *Inclusion criteria for concussive TBI subjects:*
  - Enrollment into 1 of 4 previous cohorts (see next slide)
  - Clinical diagnosis of combat concussive TBI. Including loss of consciousness, amnesia, or any change in neurological status.
  - Combat Concussion occurring in the acute to sub-acute time preceding enrollment
    0-90 days (median 14, Study 1), 0-30 days (median 7-9, Study 2&3), and 0-7 days (median 4, Study 4).
  - Evacuation to Landstuhl Regional Medical Center (LRMC) or in country evacuation to Kandahar Airfield (KAF) or Camp Leatherneck (LNK)
  - Willingness to participate in the study, ability to communicate and comply with the study protocol and ability to provide informed consent.
  - **<u>ALL PATIENTS MET THE DOD DEFINITION FOR MILD UNCOMPLICATED BRAIN INJURY</u>**
- *Inclusion criteria for combat deployed controls:*
  - Willingness to participate in the study, ability to communicate and comply with the study protocol and ability to provide informed consent.
  - No history of major TBI and no head injury identified upon evaluation at LRMC, KAF, or LNK.
- *Exclusion criteria for both groups:*
  - Life history of previous major/severe traumatic brain injury or previous psychiatric diagnoses.
  - Inability to lie still in a supine position for the duration of MRI scan sessions, e.g. no severe claustrophobia or limiting pain from other injuries.
  - Known metallic implants or metallic foreign objects.
  - Pregnancy.
  - Other contraindication to MRI because of medical reasons such as arrhythmias.

Total Enrollment from 2008 to 2013: 591

Landstuhl Regional Medical Center
Landstuhl, Germany (Medical Evacuation)

Kandahar Airfield/Camp Leatherneck
Afghanistan (No Medical Evacuation)

Study 1 (2008-2009)
0-90 days post-injury
Median: 14 days
Total: 84
Blast Control: 21
Blast TBI: 63

Study 2 (2010-2011)
0-30 days post-injury
Median: 7 days
Total: 40
Blast TBI: 40

Study 3 (2010-2013)
0-30 days post-injury
Median: 9 days
Total: 255
Non-blast Control: 97
Blast Control: 35
Non-blast TBI: 44
Blast TBI:79

Study 4 (2012)
0-7 days post-injury
Median: 4 days
Total: 212
Non-blast Control: 101
Blast TBI: 95
*Disqualified: 16

Total Completed ~1 Year Follow Up at Washington University in Saint Louis: 347

Study 1 Total: 65
Blast Control: 18
Blast TBI: 47

Study 2 Total: 32
Blast TBI: 32

Study 3 Total: 183
Non-blast Control: 69
Blast Control: 27
Non-blast TBI: 29
Blast TBI: 53
**Disqualified: 5

Study 4 Total: 72
Non-blast Control: 34
Blast TBI: 38
(100 Invited)

Total Completed ~5 Year Follow Up at University of Washington in Seattle: 342

Study 1 Total: 53
Blast Control: 18
Blast TBI: 35
Deceased: 4
(all blast TBI)

Study 2 Total: 31
Blast TBI:31
Deceased: 1
(made it to 5yr F/U)

Study 3 Total: 162
Non-blast Control: 62
Blast Control: 22
Non-blast TBI: 28
Blast TBI: 50
Deceased: 2
(1 blast CTL & 1 blast TBI)

Study 4 Total: 96
Non-blast Control: 47
Blast TBI: 49

10-Year F/U started April 2019
31 Patient Evaluations
Completed and Counting!

LANDSTUHL REGIONAL MEDICAL CENTER

WELCOME TO KANDAHAR AIRFIELD
بنه راغلاست د
کندهار هوایی ډګر ته

- **Imaged at LRMC/AFG with:**
  - Advanced MRI
    - Diffusion Tensor Imaging
    - Resting-state fMRI
  - Conventional Brain Imaging
    - MP-RAGE, T2, FLAIR, T2*/SWI

- **Travel WU/UW to be Re-imaged & evaluated**
- **Repeat MRI**
  - Evaluation
    - Neurological :
      - Glasgow Outcome Scale – Extended – Global Disability
      - Neurobehavioral Rating Scale and Promis-Pain
      - Migraine Disability Scale (MIDAS) and HIT-6
      - Neurological Outcomes for TBI (NOS-TBI)
    - Psychological:
      - PTSD : CAPS-Clinician-Administered PTSD Scale and PCL-M
      - Depression MADRS – Montgomery-Asberg Depression Rating Scale and BDI
      - MAST: Michigan Alcohol Screening Test
      - CES: Combat Exposures Scale and CD-RISC for Resiliency
      - BSI-A – Anxiety Module and Insomnia Severity Index
    - Neuropsych : 11 Test Battery of Assessments (next slide)

1 Year

Washington University in St.Louis
SCHOOL OF MEDICINE

5 Year

W 10 Year
UNIVERSITY of WASHINGTON

Neurospsychological Assessments

- Conner's Continuous Performance Test II, a computer-based assessment of attention, impulsivity, reaction time, and vigilance.

- California Verbal Learning Test II, an assessment of verbal declarative memory.

- 25 hole grooved pegboard test , an assessment of upper extremity motor speed and coordination.

- Timed 25 foot walk, an assessment of motor strength, balance, coordination.

- Trail Making test, an assessment of visual scanning, coordination and mental flexibility.

- Controlled Oral Word Association test, an assessment of verbal fluency.

- Wechsler Test of Adult Reading as an estimate of pre-injury verbal intelligence.

- Iowa Gambling Test, a computer-based assessment of impulsivity and decision making.

- Ruff-Light Trail Learning Test, an assessment of visual-spatial memory.

- D-KEFS Color-Word Interference Test, an multi-domain assessment of executive function.

- Frontal Systems Behavior Scale (FrSBe) a self administered assessment of apathy, disinhibition, executive dysfunction (Completed by Patient and Collateral Source)
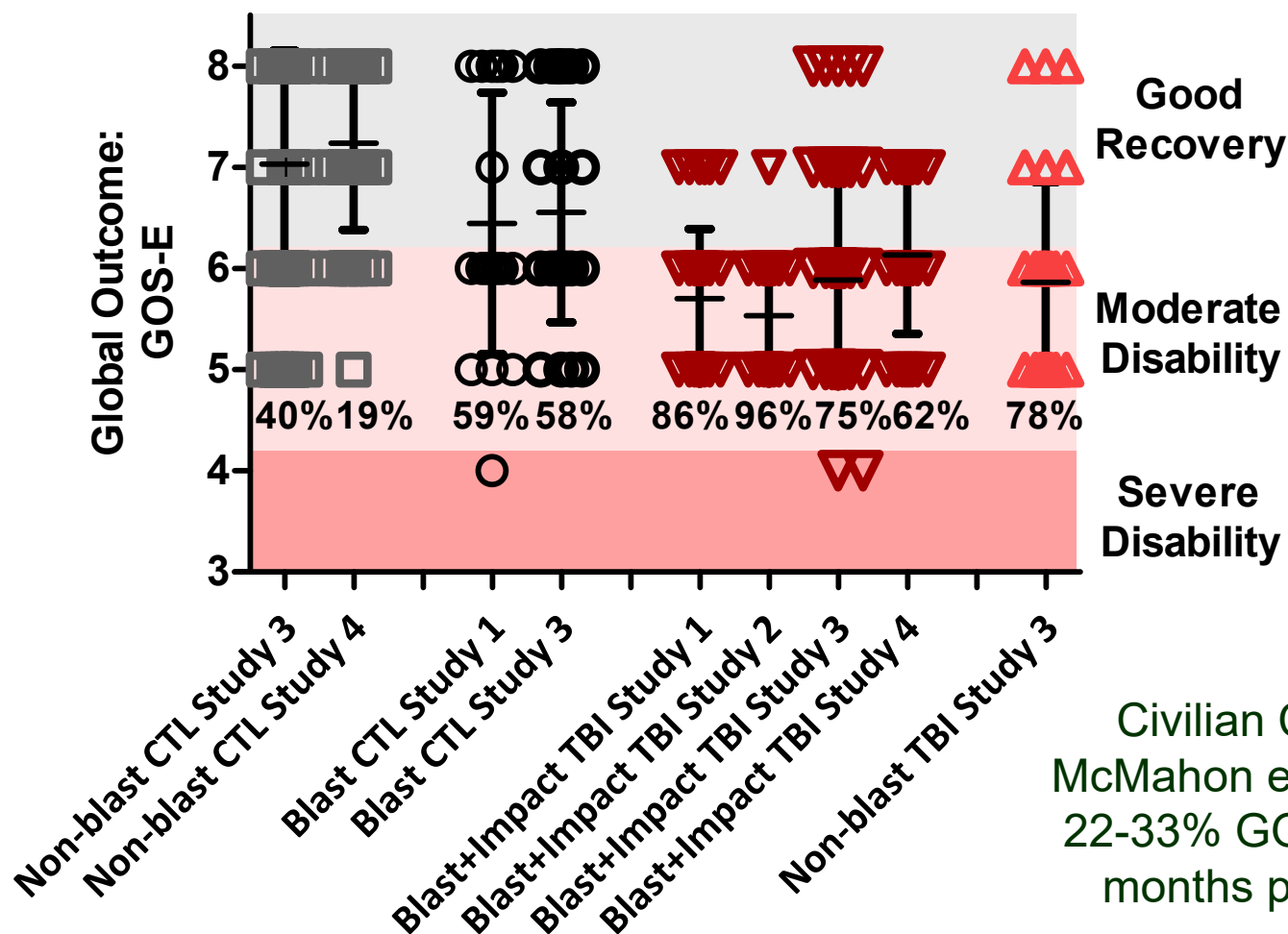
Clinical Outcomes Following Combat Concussion

Findings from the EVOLVE Study
1-year and 5-year Follow Up

Global Disability at ~1 Year Follow Up

Global Outcome: GOS-E

Good Recovery

Moderate Disability

Severe Disability

40% 19%   59% 58%   86% 96% 75% 62%   78%

Non-blast CTL Study 3
Non-blast CTL Study 4
Blast CTL Study 1
Blast CTL Study 3
Blast+Impact TBI Study 1
Blast+Impact TBI Study 2
Blast+Impact TBI Study 3
Blast+Impact TBI Study 4
Non-blast TBI Study 3

Civilian Comparison:
McMahon et al JNTA 2014:
22-33% GOS-E<6 at 6-12
months post 'mild' TBI

Take home message:
1. **Combat Concussion is worse repeated across FOUR different cohorts.**
2. **No distinction between Blast & Non-blast TBI,**
3. **No distinction between med-evac (Study 1-3) and non-med-evac (Study 4) Combat Concussion**
4. **Interestingly, Blast Control DOES differ from Non-blast Control**

Mac Donald, et al, J Neurotrauma 2017

Depression & PTSD Symptoms at ~1 year Follow Up

Dashed line indicates cutoff for moderate/severe symptoms

p < 0.0000001

Kruskal-Wallis ANOVA

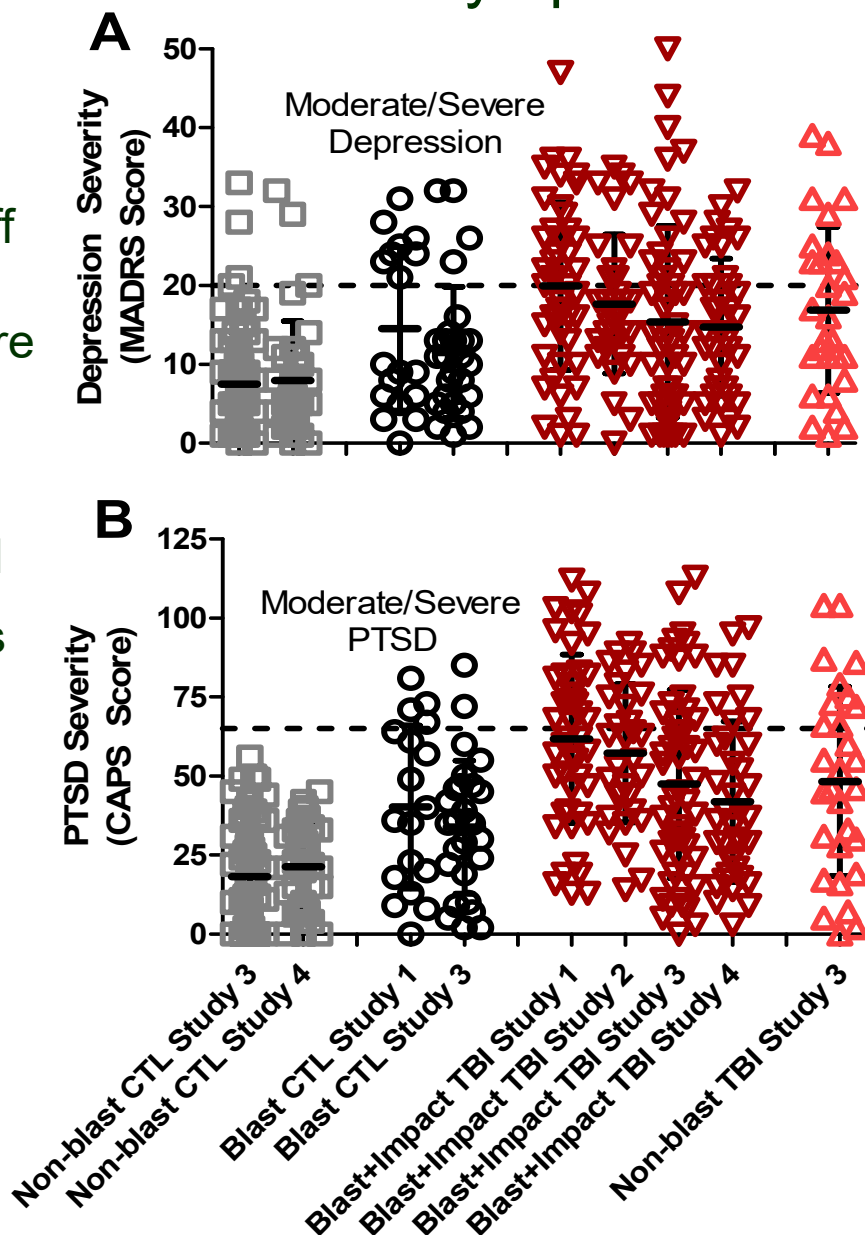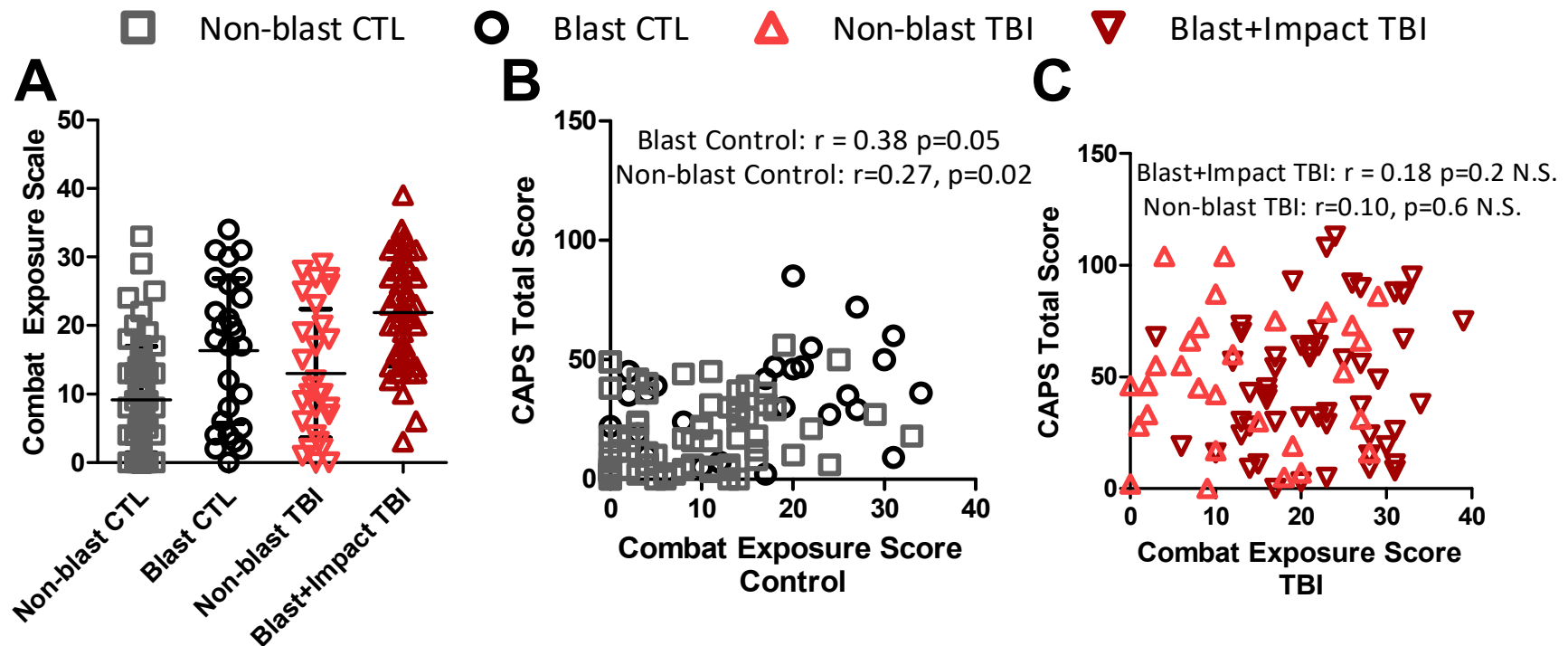**Take home message:**

1. Combat Concussion is worse repeated across FOUR different cohorts.

2. No distinction between Blast & Non-blast TBI.

3. No distinction between med-evac (Study 1-3) and non-med-evac (Study 4) Combat Concussion

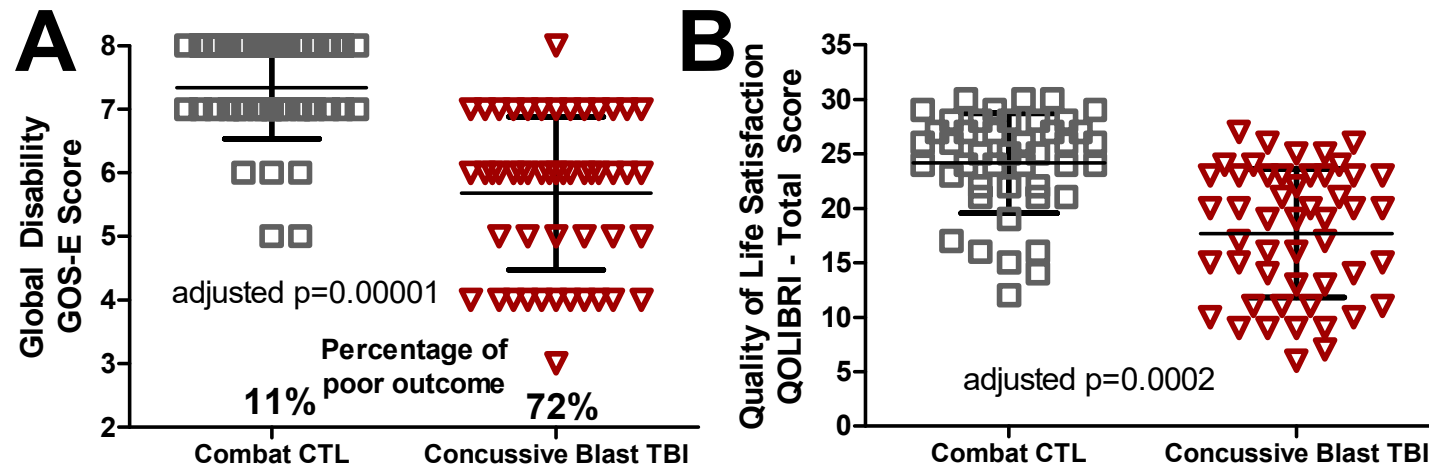**4. Interestingly, Blast Control DOES differ from Non-blast Control**

Mac Donald, et al, J Neurotrauma 2017

Relationship of PSTD to Intensity of Combat Exposure

Legend: □ Non-blast CTL   ○ Blast CTL   △ Non-blast TBI   ▽ Blast+Impact TBI

A Combat Exposure Scale (Non-blast CTL, Blast CTL, Non-blast TBI, Blast+Impact TBI)

B CAPS Total Score vs Combat Exposure Score Control
Blast Control: r = 0.38 p=0.05
Non-blast Control: r=0.27, p=0.02

C CAPS Total Score vs Combat Exposure Score TBI
Blast+Impact TBI: r = 0.18 p=0.2 N.S.
Non-blast TBI: r=0.10, p=0.6 N.S.
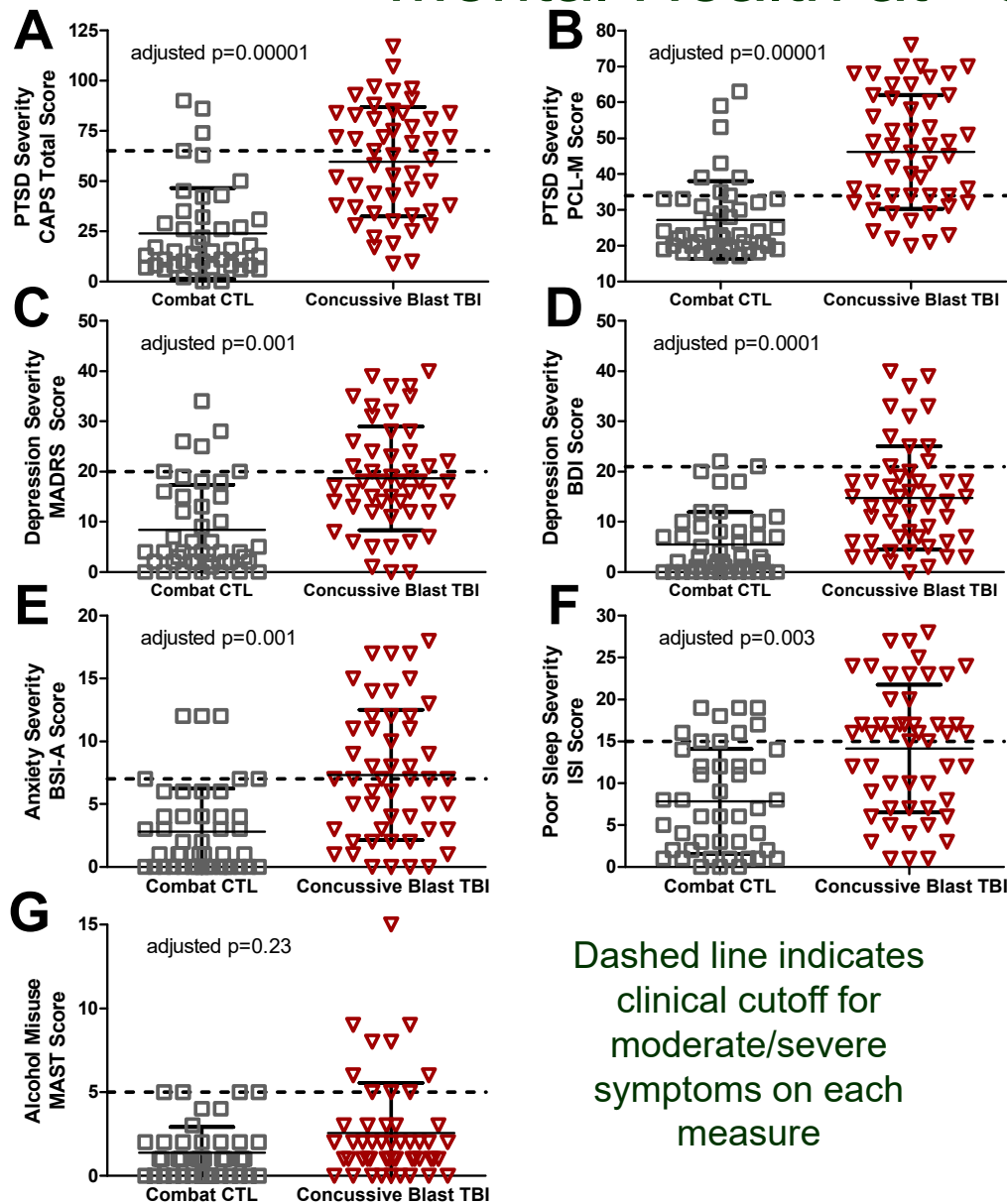
Take home message:

1. The relationship between combat exposure and PTSD severity is differentially related to TBI subjects in comparison to Controls.

2. In the presence of mild TBI, 'something' changes and the brain injury seems to be more impacting on PTSD symptomatology than the intensity of combat exposure.

Mac Donald et al, JAMA Neurology, 2014

Global Disability at ~5 year follow up

A — Global Disability GOS-E Score; Combat CTL vs Concussive Blast TBI; adjusted p=0.00001; Percentage of poor outcome 11% vs 72%

B — Quality of Life Satisfaction QOLIBRI - Total Score; Combat CTL vs Concussive Blast TBI; adjusted p=0.0002

- Overall disability and quality of life were significantly impacted in the concussive blast group compared to combat-deployed controls

- Comparing 1-year with 5-year GOS-E scores in the very same participant, 11% of combat-deployed controls and 72% of concussive blast patients experienced a substantial decline by their 5-year evaluation.
  - Substantial decline was defined as 1 year score in the good recovery range and a 5 year score in the moderate to severe disability range or a step down from moderate disability to severe disability in that same time frame.

Mac Donald, et al, JAMA Neurology 2017

Mental Health at ~5 year follow up

A — adjusted p=0.00001 — PTSD Severity CAPS Total Score — Combat CTL / Concussive Blast TBI

B — adjusted p=0.00001 — PTSD Severity PCL-M Score — Combat CTL / Concussive Blast TBI

C — adjusted p=0.001 — Depression Severity MADRS Score — Combat CTL / Concussive Blast TBI

D — adjusted p=0.0001 — Depression Severity BDI Score — Combat CTL / Concussive Blast TBI

E — adjusted p=0.001 — Anxiety Severity BSI-A Score — Combat CTL / Concussive Blast TBI

F — adjusted p=0.003 — Poor Sleep Severity ISI Score — Combat CTL / Concussive Blast TBI

G — adjusted p=0.23 — Alcohol Misuse MAST Score — Combat CTL / Concussive Blast TBI

Dashed line indicates clinical cutoff for moderate/severe symptoms on each measure
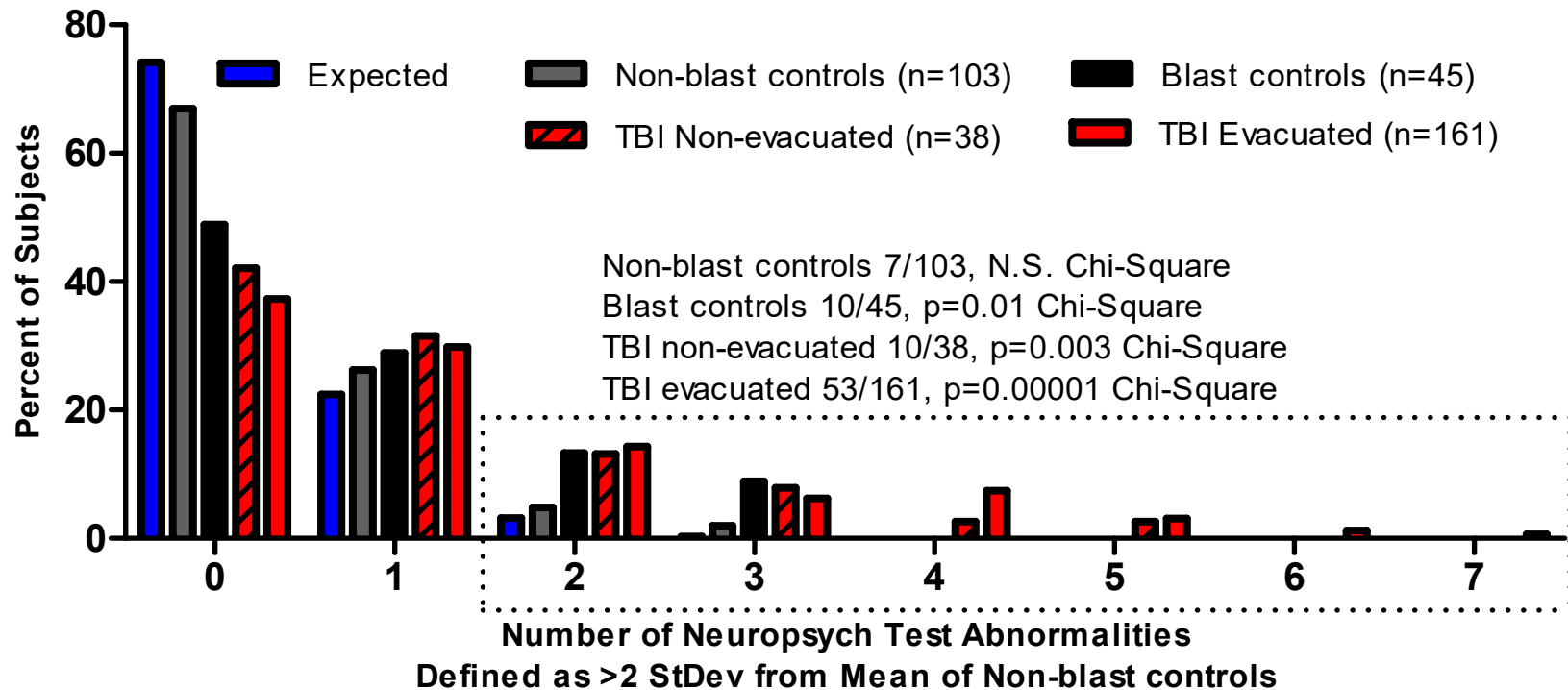
Mac Donald, et al, JAMA Neurology 2017

- Concussive blast patients had significant elevations in measures of PTSD, depression, anxiety and poor sleep compared to combat-deployed controls.

- Alcohol misuse was NOT significantly different.

- Surprising to us, 41% combat controls and 80% of concussive blast patients endorsed seeking help for their mental health symptoms BUT only 19% of each group found sustained resolution

Cognitive Performance 1-year Post-Injury

Legend:
- Expected (blue)
- Non-blast controls (n=103) (gray)
- Blast controls (n=45) (black)
- TBI Non-evacuated (n=38) (red hatched)
- TBI Evacuated (n=161) (red)

Non-blast controls 7/103, N.S. Chi-Square
Blast controls 10/45, p=0.01 Chi-Square
TBI non-evacuated 10/38, p=0.003 Chi-Square
TBI evacuated 53/161, p=0.00001 Chi-Square

Y-axis: Percent of Subjects

X-axis: Number of Neuropsych Test Abnormalities
Defined as >2 StDev from Mean of Non-blast controls

Take home message:
1. No group level differences in cognitive performance across any of the groups
2. A subset of patients within each group did exhibit deficits on some of the cognitive tests
3. No distinction in the number of combat concussion patients in this subset per group between med-evac (TBI evacuated) and non-med-evac (TBI non-evacuated)
4. Interestingly, Blast Control did show a significantly greater number of subset of participants with deficits than would have been expected by chance.

Mac Donald, et al, J Neurotrauma 2016

eTable 1. Neuropsychological Test Performance at 5-Year Follow-Up

Assessment	Combat CTL (n=44)	Concussive Blast TBI (n=50)	Adjusted P Value
25-Foot Walk (seconds): *Motor Strength, Balance, Coordination*	4.03 ± 0.71	4.25 ± 1.14	.32
Conners' Continuous Performance Test III			
Omission Errors (T-score): *Attention Lapses*	46.66 ± 6.29	47.86 ± 7.59	.61
Commission Errors (T-score): *Impulsivity*	49.39 ± 8.74	51.34 ± 10.02	.54
Hit Rate (T-score): *Reaction Time*	50.07 ± 5.95	51.24 ± 7.59	.75
Hit Rate Block Change (T-score): *Sustained Vigilance*	51.34 ± 8.91	52.44 ± 10.89	.49
Wechsler Test of Adult Reading (Standard Score) *(Estimate of Pre-injury Verbal Intelligence)*	107.32 ± 12.09	104.66 ± 10.84	.62
California Verbal Learning Test II			
Long-Delay Free Recall (Standard Score): *Verbal Memory*	0.16 ± 1.00	-0.24 ± 1.01	.14
Total Intrusions (Standard Score): *Falsely Recalled Items*	0.08 ± 1.11	0.21 ± 1.01	.99
List B vs. List A (Standard Score): *Proactive Memory Interference*	-0.24 ± 1.33	-0.05 ± 0.99	.44
Ruff Light Trail Learning Test			
Total Trials Correct (T-score): *Visuospatial Learning*	50.98 ± 9.74	47.44 ± 11.34	.05
Long Delay Trial Correct: *Visuospatial Memory*	14.36 ± 0.97	13.84 ± 1.71	.12
Grooved Pegboard (Motor Speed & Coordination)			
Average Dom & Non-Dom Time (seconds)	67.49 ± 8.77	72.29 ± 10.89	.07
Trail Making Test			
Trails A time (seconds): *Visual Scanning, Coordination*	21.85 ± 6.02	23.93 ± 10.31	.58
Trails B time (seconds): *Mental Flexibility*	56.37 ± 15.65	63.16 ± 24.02	.05
Controlled Oral Word Association Total Score: *Verbal Fluency*	46.11 ± 10.67	40.66 ± 9.62	.04
DKEFS Color Word Interference: *Executive Function*			
Trial 1 + Trial 2 (scaled score): *Naming, Reading*	20.07 ± 4.99	18.72 ± 6.36	.82
Trial 3 (scaled score): *Inhibition*	11.16 ± 2.57	9.68 ± 3.24	.30
Trial 4 (scaled score): *Inhibition Switching*	10.74 ± 2.12	9.08 ± 3.65	.11
Iowa Gambling Task Net Trials (T-score): *Monetary decision making*	50.41 ± 10.48	48.54 ± 10.13	.38

Mac Donald et al JAMA Neurology 2017

No significant differences in cognitive performance 5 years post-injury across groups

QUESTION: Are there Acute Predictors of 5-Year Outcome?

?

QUESTION: Could neuroimaging help us understand whether there were brain specific changes contributing to this clinical decline observed from 1-year to 5-years?

Acute Predictors of 5-Year Outcome

Clinical Variables Collected 0-7 Days in Afghanistan

Neurobehavior/Concussion Symptoms
1. Rivermead Post Concussion Symptoms Questionnaire a brief questionnaire capturing concussion symptoms.
2. Balance Error Scoring System, a basic assessment of static postural stability.

Psychiatric Evaluation
1. PTSD Checklist-Military (PCL-M) a brief questionnaire capturing PSTD symptoms.
2. Beck Depression Inventory (BDI) a brief questionnaire capturing depression symptoms.
3. Combat Exposures Scale an assessment of the intensity of combat exposure during deployment.

Neuropsychological Exam.
Automated Neuropsychological Assessment Metrics (ANAM)
-Reaction Time
-Reaction Time – Repeat
-Processing Speed
-Associative Learning
-Delayed Memory
-Working Memory
-Visual Spatial Memory
-Sleep

Participant Characteristics at 5-Year Follow Up			
Characteristic	Combat Control (n=45)	Concussive Blast TBI (n=45)	P-Value
Age in years:			
mean (stdev)	34.4 ± 6.7	30.6 ± 5.3	.004
Education in years:			
mean (stdev)	16.6 ± 3.4	13.6 ± 1.7	<.001
Gender - no (%)			
Male	33 (73%)	44 (98%)	.002
Female	12 (27%)	1 (2%)	
Race/ethnicity - no (%)			
White	35 (78%)	32 (72%)	
African American	3 (7%)	2 (4%)	.63
Hispanic/Latino	7 (15%)	10 (22%)	
Asian	0 (0%)	1 (2%)	
Branch of Service - no (%)			
US Army	13 (29%)	39 (87%)	
US Air Force	5 (11%)	0 (0%)	<.001
US Marine Corps	5 (11%)	5 (11%)	
US Navy	22 (49%)	1 (2%)	
Military Rank - no (%)			
Enlisted	29 (64%)	43 (96%)	.001
Officer	16 (36%)	2 (4%)	
Number of Deployments	1.55 ± 0.87	1.84 ± 1.22	.22
Service Separation - no (%)	16 (36%)	27 (60%)	.03

Statistical significance by Mann-Whitney or Fisher's exact test as appropriate

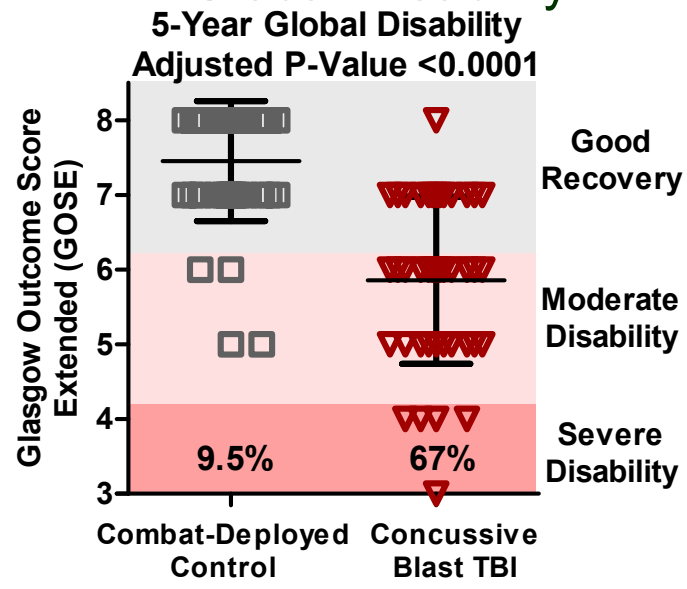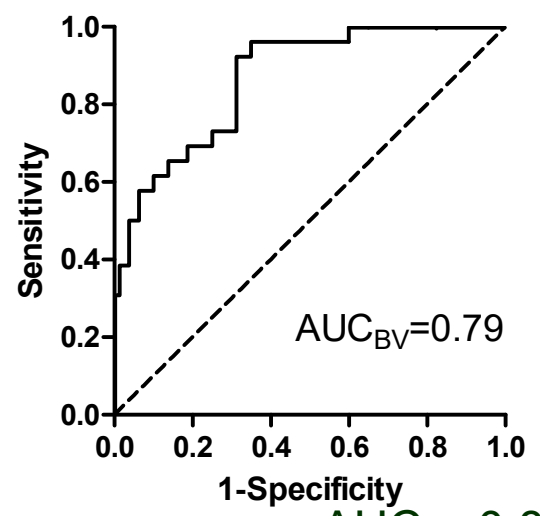Question: What early measures would best predict 4 primary domains of 5-year outcome?

-Global Disability
-Neurobehavioral Impairment
-Psychological Burden
-Cognitive Function

5 Years Post-Injury:
Global Disability in Non-Medically Evacuated Blast Concussion

5-Year Global Disability Adjusted P-Value <0.0001

Good Recovery

Moderate Disability

Severe Disability

9.5% 67%

Glasgow Outcome Score Extended (GOSE)

Combat-Deployed Control   Concussive Blast TBI

0-7 Day Logistic Regression Predictors of 5-Year Poor Global Outcome

$AUC_{BV}=0.79$

Logistic Regression Prediction of 5-Year Poor Global Outcome (GOSE 6 or Less vs. GOSE 7-8)					
	0-7 Day Predictors	**Univariate**		**Multivariate**	
		OR	p-value	OR	p-value
Demographics & 0-7 Day Outcomes	Age in Combat	0.92	0.03		0.46
	Officer vs. Enlisted	0.07	0.01		0.13
	Female vs. Male	0.24	0.08		0.59
	Branch of Service	6.72	<.001		0.68
	TBI Diagnosis	16	<.001	7.86	0.001
	Number of Deployments	0.99	0.96		0.48
	Number of Subsequent Concussions	2.01	0.01		0.13
	Concussion Symptoms (RPCSQ)	1.1	<.001	1.06	0.008
	PTSD Symptom Severity (PCL-M)	1.09	<.001		0.52
	Depression Symptom Severity (BDI)	1.13	0.001		0.95
	Combat Intensity (CES)	1.09	<.001		0.96
	Postural Stability (BESS)	1.01	0.77		0.32
0-7 Day ANAM Testing	Sleep Impairment	1.93	0.001		0.98
	Simple Reaction Time	1.01	0.07		0.88
	Simple Reaction Time -R	1	0.5		0.93
	Processing Speed (PRT)	0.98	0.15		0.19
	Associative Learning (CSL)	0.97	0.09		0.94
	Delayed Memory (CSD)	0.97	0.11		0.76
	Working Memory (MTP)	0.92	0.02		0.86
	Visuospatial Memory (MTS)	0.96	0.05		0.15

AUC = 0.80 is considered strong prediction strength

Mac Donald et al, JAMA Network Open 2019
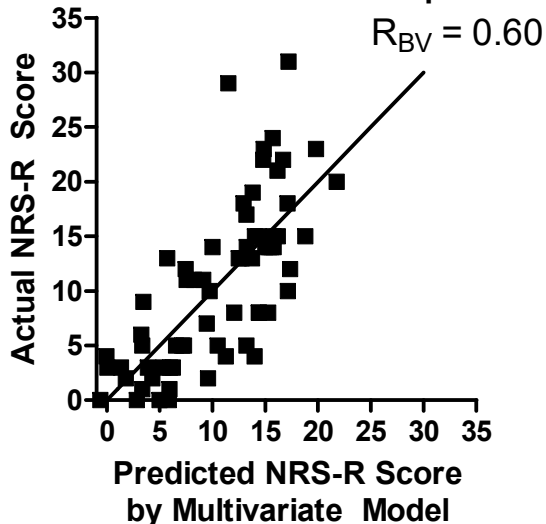
5 Years Post-Injury:
Neurobehavior Impairment in Non-Medically Evacuated Blast Concussion

5-Year Neurobehavioral Impairment Adjusted P-Value <0.001
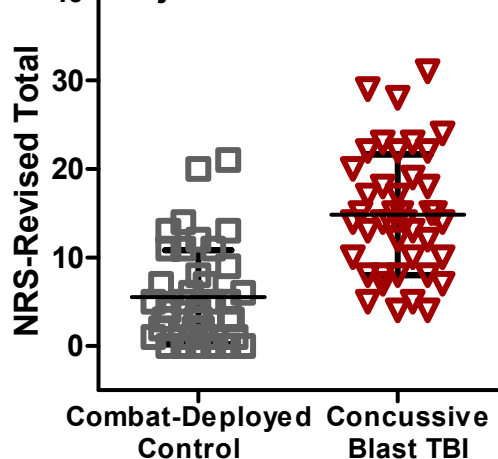
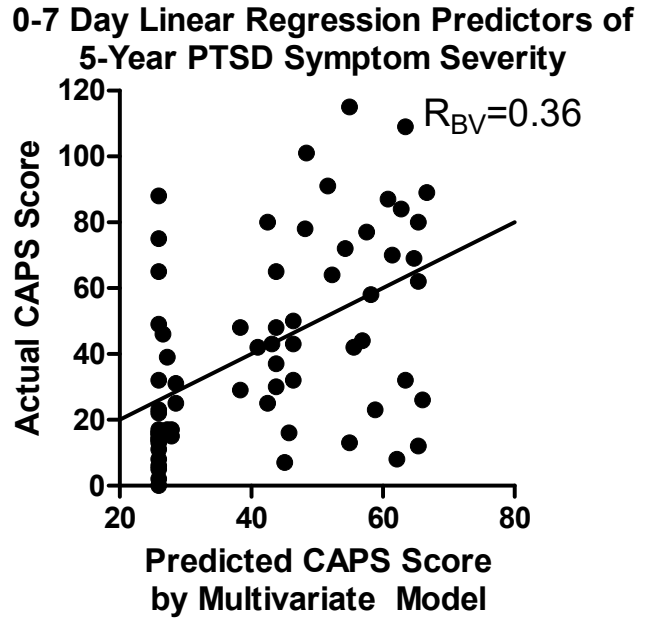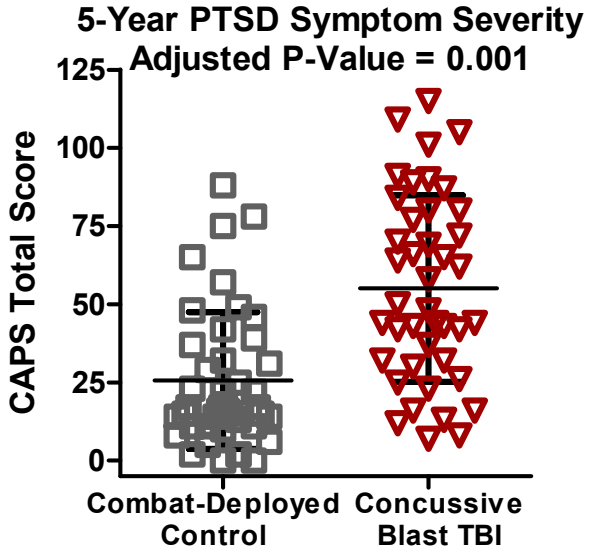**0-7 Day Linear Regression Predictors of 5-Year Neurobehavioral Impairment**

$R_{BV} = 0.60$

Linear Regression Prediction of 5-Year Neurobehavioral Impairment					
	0-7 Day Predictors	**Univariate**		**Multivariate**	
		B	p-value	B	p-value
Demographics & 0-7 Day Outcomes	Age in Combat	-0.32	0.01		0.96
	Officer vs. Enlisted	-8.29	<.001	-4.6	0.004
	Female vs. Male	-5.53	0.01		0.84
	Branch of Service	5.2	0.001		0.73
	TBI Diagnosis	9.13	<.001	7.01	<.001
	Number of Deployments	0.49	0.35		0.7
	Number of Subsequent Concussions	2.09	0.02		0.52
	Concussion Symptoms (RPCSQ)	0.29	<.001		0.28
	PTSD Symptom Severity (PCL-M)	0.27	<.001		0.4
	Depression Symptom Severity (BDI)	0.41	<.001	0.25	0.006
	Combat Intensity (CES)	0.34	<.001		0.5
	Postural Stability (BESS)	0.05	0.65		0.39
0-7 Day ANAM Testing	Sleep Impairment	2.16	<.001		0.72
	Simple Reaction Time	0.01	0.27		0.24
	Simple Reaction Time -R	0.01	0.27		0.89
	Processing Speed (PRT)	-0.07	0.13	0.1	0.02
	Associative Learning (CSL)	-0.06	0.29		0.75
	Delayed Memory (CSD)	-0.05	0.34		0.71
	Working Memory (MTP)	-0.3	0.007		0.72
	Visuospatial Memory (MTS)	-0.21	0.003	-0.19	0.001

R = 0.6 is considered strong prediction strength

Mac Donald et al, JAMA Network Open 2019

5 Years Post-Injury:
PTSD Symptom Severity in Non-Medically Evacuated Blast Concussion

5-Year PTSD Symptom Severity
Adjusted P-Value = 0.001

0-7 Day Linear Regression Predictors of 5-Year PTSD Symptom Severity

$R_{BV}=0.36$

Linear Regression Prediction of 5-Year PTSD Symptom Severity			Univariate		Multivariate	
	0-7 Day Predictors		**B**	**p-value**	**B**	**p-value**
Demographics & 0-7 Day Outcomes	Age in Combat		-1.03	0.03		0.39
	Officer vs. Enlisted		-26.65	<.001		0.05
	Female vs. Male		-16.74	0.06		0.95
	Branch of Service		17.97	0.003		0.69
	TBI Diagnosis		28.18	<.001	17.59	0.006
	Number of Deployments		0.88	0.66		0.87
	Number of Subsequent Concussions		7.02	0.04		0.37
	Concussion Symptoms (RPCSQ)		1.11	<.001	0.72	0.004
	PTSD Symptom Severity (PCL-M)		1.07	<.001		0.31
	Depression Symptom Severity (BDI)		1.66	<.001		0.38
	Combat Intensity (CES)		1.17	<.001		0.37
	Postural Stability (BESS)		0.04	0.92		0.27
0-7 Day ANAM Testing	Sleep Impairment		7.9	0.001		0.95
	Simple Reaction Time		0.03	0.27		0.31
	Simple Reaction Time -R		0.03	0.17		0.32
	Processing Speed (PRT)		-0.21	0.25		0.26
	Associative Learning (CSL)		-0.14	0.55		0.32
	Delayed Memory (CSD)		-0.31	0.14		0.83
	Working Memory (MTP)		-0.97	0.02		0.69
	Visuospatial Memory (MTS)		-0.29	0.28		0.71

R = 0.3-0.4 is considered moderate prediction strength

Mac Donald et al, JAMA Network Open 2019

5 Years Post-Injury:
Cognitive Performance in Non-Medically Evacuated Blast Concussion

5-Year Cognitive Performance Adjusted P-Value = 0.56

0-7 Day Linear Regression Predictors of 5-Year Cognitive Test Performance

$R_{BV}=0.34$
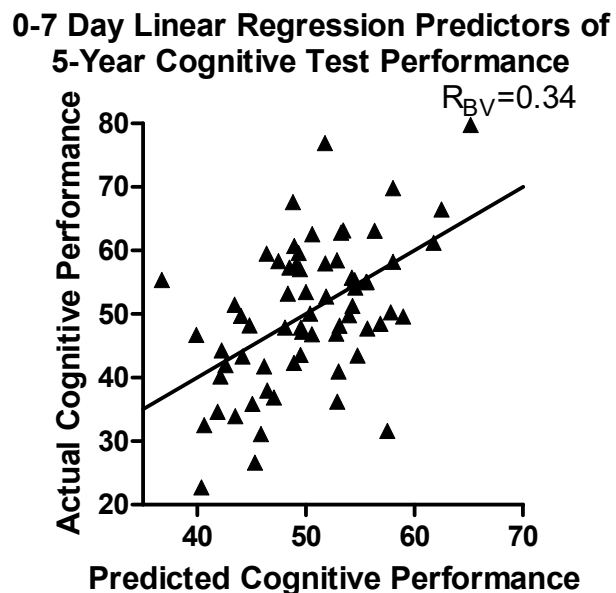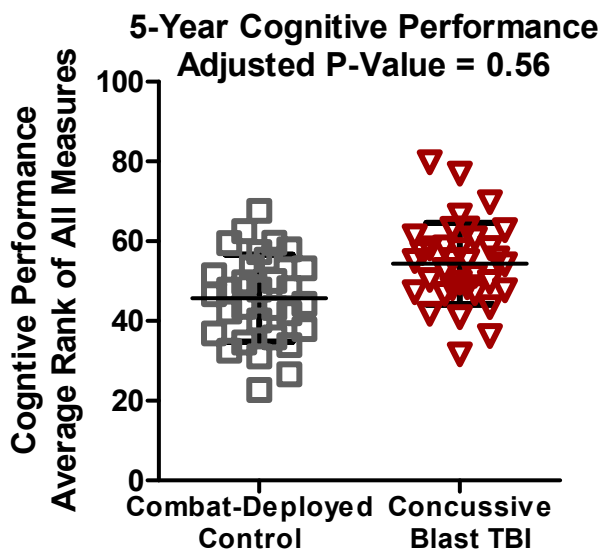
Linear Regression Prediction of 5-YearCognitive Performance

	0-7 Day Predictors	Univariate B	Univariate p-value	Multivariate B	Multivariate p-value
Demographics & 0-7 Day Outcomes	Age in Combat	-0.36	0.03		0.68
	Officer vs. Enlisted	-6.08	0.01		0.5
	Female vs. Male	-5.5	0.05		0.89
	Branch of Service	5.62	0.005		0.58
	TBI Diagnosis	7.7	<.001	5.35	0.007
	Number of Deployments	0.25	0.77		0.56
	Number of Subsequent Concussions	1.19	0.28		0.76
	Concussion Symptoms (RPCSQ)	0.14	0.06		0.74
	PTSD Symptom Severity (PCL-M)	0.17	0.03		0.8
	Depression Symptom Severity (BDI)	0.14	0.34		0.92
	Combat Intensity (CES)	0.19	0.05		0.86
	Postural Stability (BESS)	-0.18	0.16	-0.27	0.02
0-7 Day ANAM Testing	Sleep Impairment	1.85	0.02		0.82
	Simple Reaction Time	0.01	0.48		0.42
	Simple Reaction Time -R	0.01	0.29		0.59
	Processing Speed (PRT)	-0.16	0.006		0.17
	Associative Learning (CSL)	-0.16	0.04		0.47
	Delayed Memory (CSD)	-0.14	0.04		0.2
	Working Memory (MTP)	-0.58	<.001	-0.45	0.001
	Visuospatial Memory (MTS)	-0.19	0.03		0.41

R = 0.3-0.4 is considered moderate prediction strength

Mac Donald et al, JAMA Network Open 2019

Summary of Clinical Outcome Results

- Combat concussion appears to worsen global outcome at 5 year follow up even in those NOT medically evacuated from theatre.

- Combat Concussion appears to exacerbate symptoms of mental health beyond combat exposure.

- There was an evolution NOT resolution of symptoms from combat to 5 year follow up.

- Operationalizing Findings for the Mild TBI Injured War Fighter in Combat:
  - Following combat concussion, screening for PTSD symptoms within 0-7 days post-injury enhanced predictive ability of 5-year outcome.
  - Interestingly the PCL-M cut point (score of 27) was found to be much lower than the currently utilized clinical threshold (score of 35).
  - The PCL-M can be completed within 1-2 minutes supporting its utility in an acute triage environment with very low patient test burden allowing for focused early intervention.

?

Could neuroimaging help us understand whether there were brain specific changes contributing to this clinical decline observed from 1-year to 5-years?
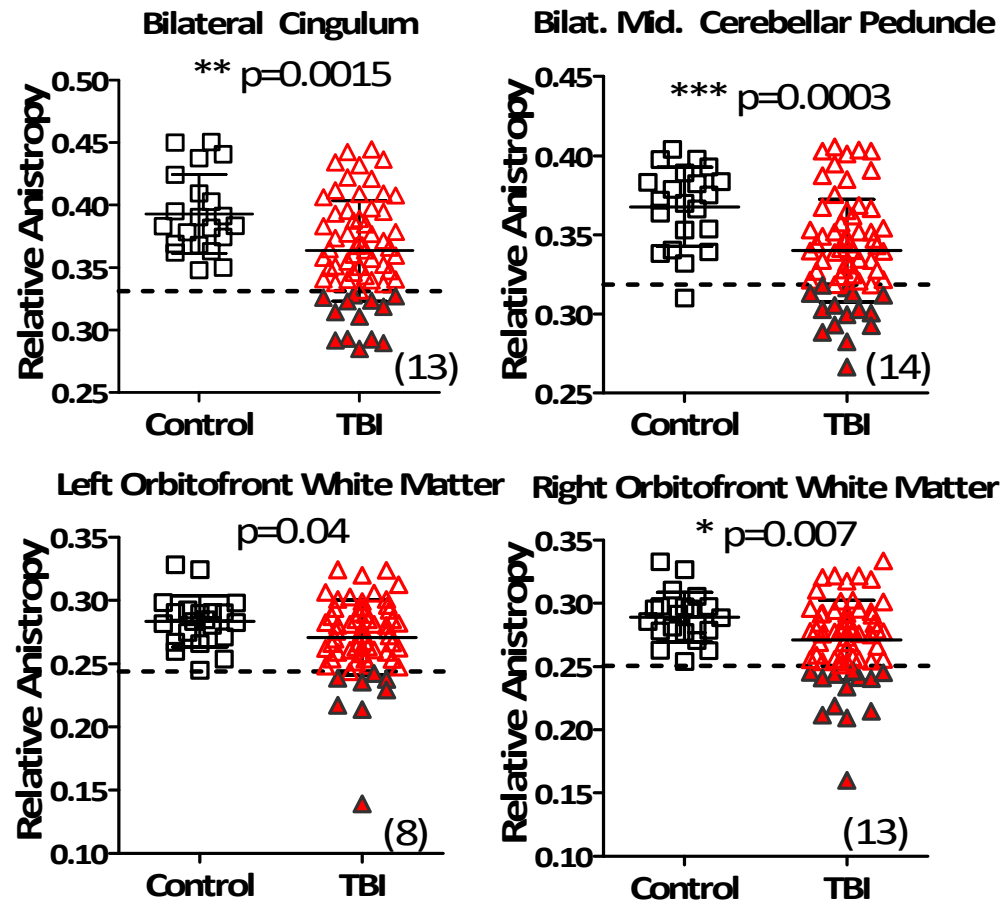
Longitudinal Conventional Imaging Findings Related to Brain Injury

NO abnormalities related to TBI were observed on the conventional images acquired at the same time as determined by a board-certified neuroradiologist
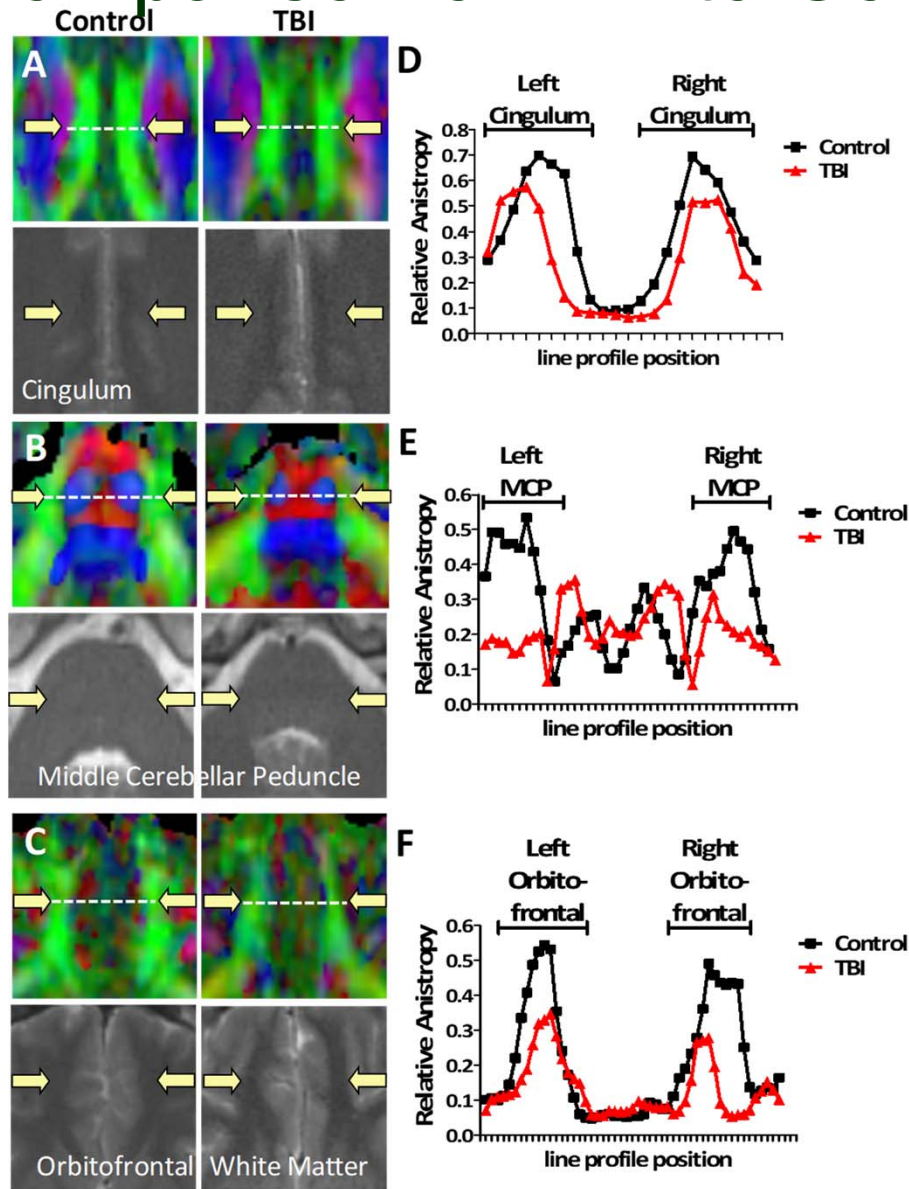
What about DTI and Quantitative Volumetrics?

DTI Abnormalities following Concussive TBI

Bilateral Cingulum
** p=0.0015

Bilat. Mid. Cerebellar Peduncle
*** p=0.0003

Left Orbitofront White Matter
p=0.04

Right Orbitofront White Matter
* p=0.007

Dashed lines indicated 2 SD below mean control

Comparison of DTI to Conventional MRI

Results are useful even on a single subject level.

Mac Donald et al, New England Journal of Medicine 2011

Follow-up Scans 6-12 Months Later: Evolution, not Resolution of DTI Abnormalities

A Initial Scans (Average 14 Days Post-Injury)
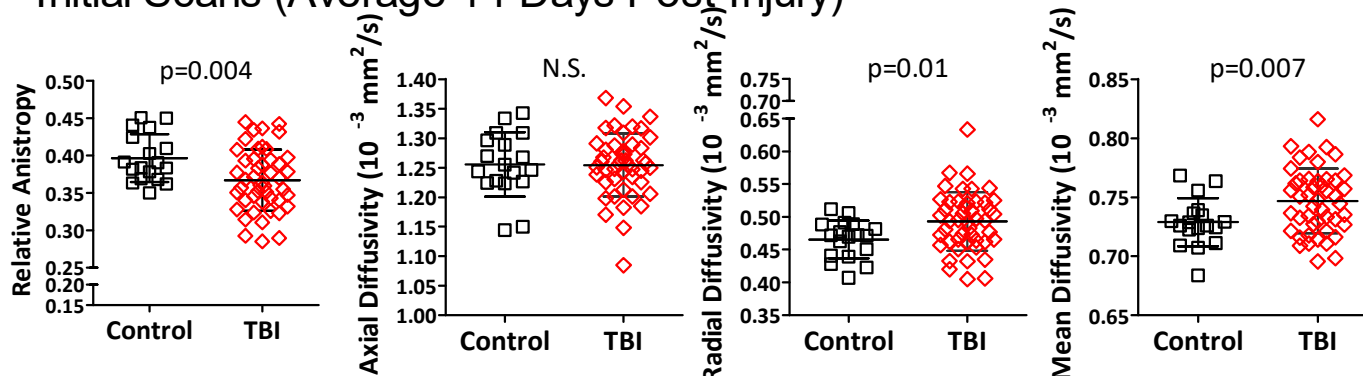
B Follow-up Scans (Average 254 days, ~8.5 months Post-Injury)
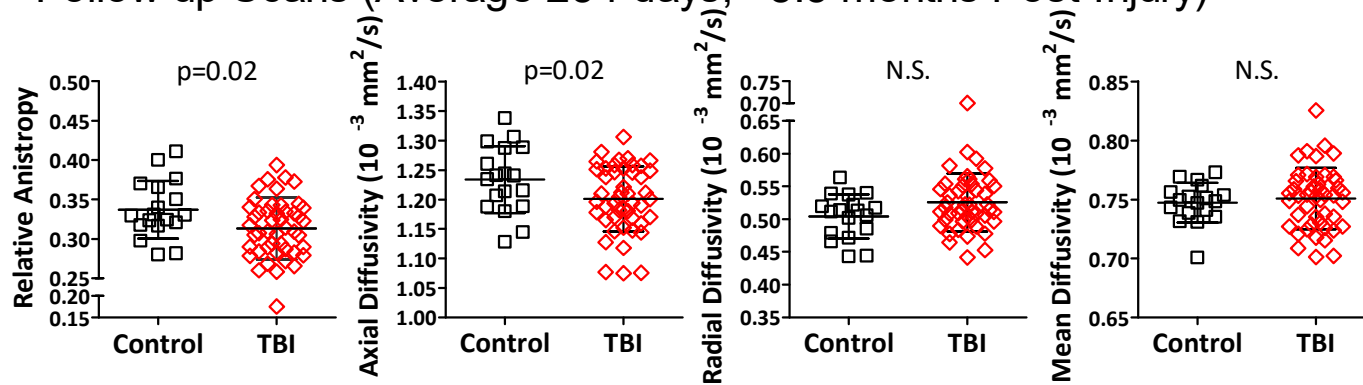
C

	Relative Anisotropy	Axial Diffusivity	Radial Diffusivity	Mean Diffusivity	Interpretation
Initial Scans	↓↓	≈	↑	↑	*Axonal Injury + Edema & Cellular Inflammation*
Follow-up Scans	↓	↓	≈	≈	*Axonal Injury (Edema & Inflammation Resolved)*

Mac Donald et al, New England Journal of Medicine 2011

5yr Follow up Group Level DTI and Quantitative Volumetric Results

A External capsule right
adjusted p=0.003

B Posterior limb of internal capsule right
adjusted p=0.002

C Middle frontal gyrus (white matter) right
adjusted p=0.003
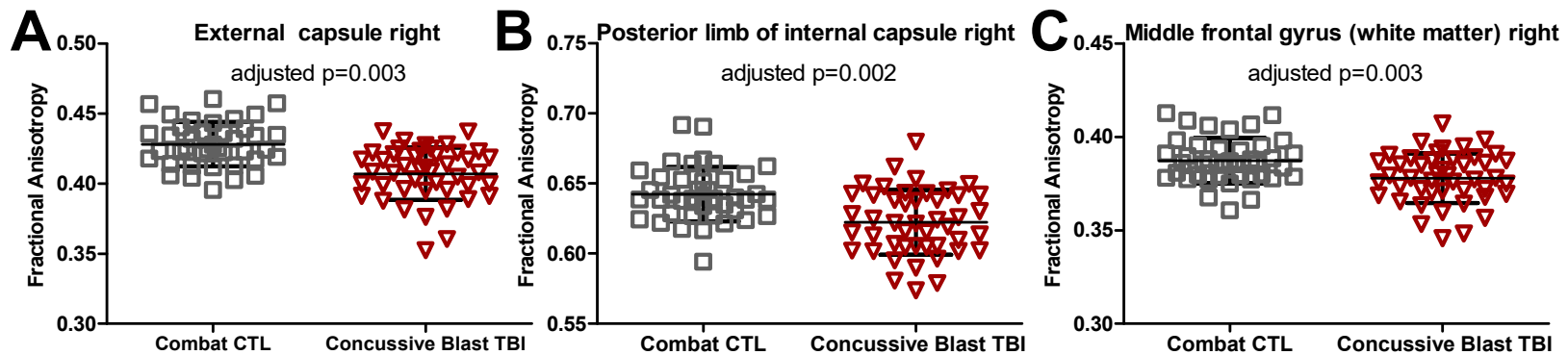
Table 2. Volumetric Analysis			
Region (volume in mm³)	Combat CTL	Concussive Blast TBI	Adjusted P-value
Total Intracranial Volume	1551448 ± 137596	1552199 ± 121377	0.78
Total Cortex Volume	486964 ± 46368	497723 ± 40154	0.87
Total Cortical White Matter Volume	503029 ± 50826	486445 ± 50752	0.17
Left Thalamus	8617 ± 785	8847 ± 886	0.46
Right Thalamus	7526 ± 677	7518 ± 556	0.64
Left Caudate	3866 ± 514	3822 ± 441	0.91
Right Caudate	3939 ± 504	3880 ± 462	0.96
Left Putamen	5826 ± 633	5863 ± 560	0.95
Right Putamen	5461 ± 558	5595 ± 485	0.86
Left Pallidum	1594 ± 196	1572 ± 197	0.59
Right Pallidum	1741 ± 167	1724 ± 183	0.80
Left Hippocampus	4355 ± 376	4351 ± 438	0.75
Right Hippocampus	4515 ± 476	4442 ± 423	0.58
Left Amygdala	1609 ± 181	1613 ± 193	0.95
Right Amygdala	1783 ± 227	1783 ± 195	0.82

Mac Donald, et al, NeuroImage:Clinical 2017

5 year follow up DTI abnormalities by Patient following blast concussion
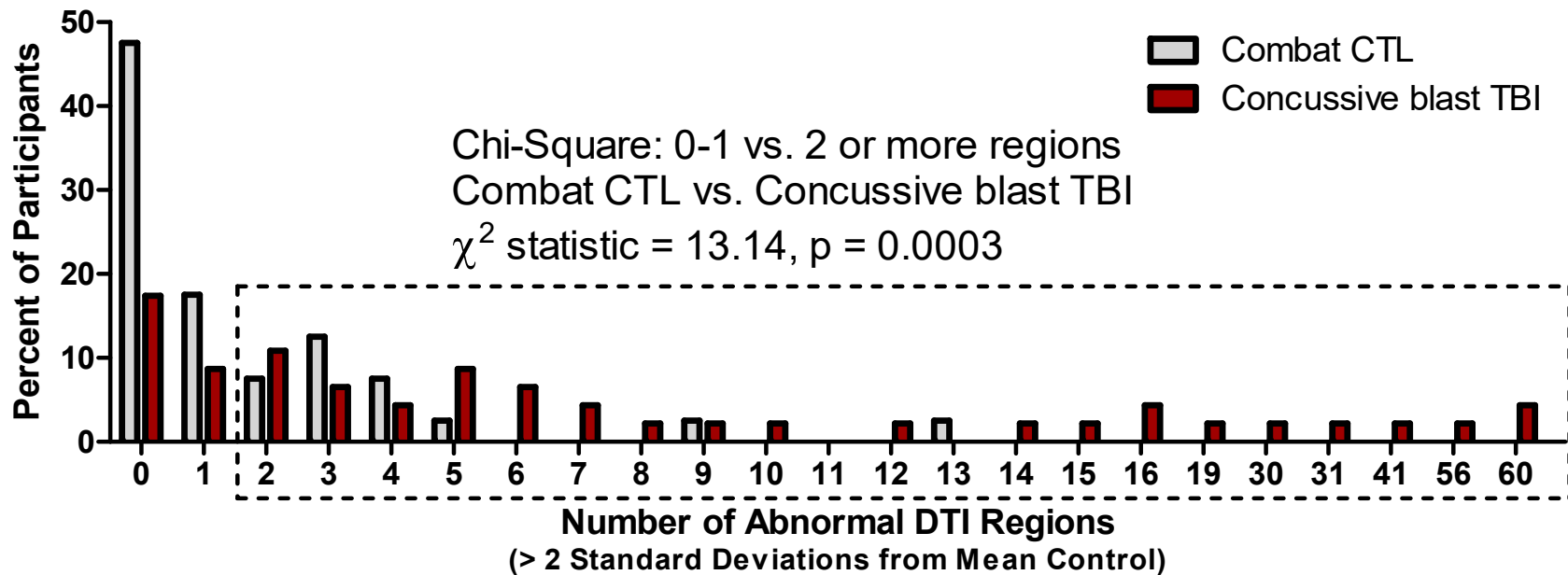
Considering the heterogeneity of brain injury and counting number of abnormal regions at the single-subject level identified 74% of the concussive blast TBI cohort to have reductions in fractional anisotropy indicative of chronic brain injury

Mac Donald, et al, NeuroImage:Clinical 2017

Clinical Predictors of Imaging Outcome at ~5 year follow up

1-year Clinical Predictors of 5-year Imaging Outcome

AUC=0.8

(Plot: Sensitivity vs 1-Specificity)
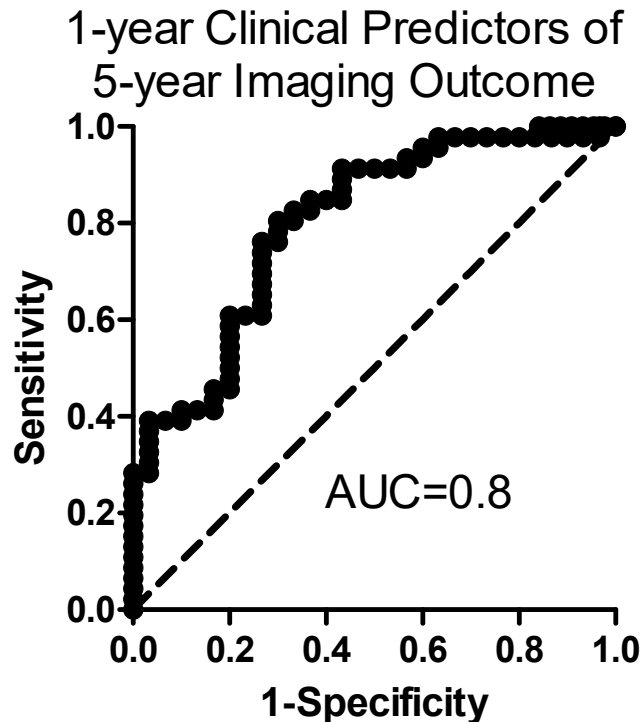
Best 1-Year Predictors of 5-Year DTI Imaging Sequelae of TBI				
Parameter	Odds Ratio	95% Confidence Interval	P-value	Predictor Direction
Clinical Status: Control or TBI	10.55	(2.25 : 49.37)	0.003	TBI Diagnosis
Age at Injury	1.14	(1.04 : 1.25)	0.008	Older Age
Depression Symptoms	0.95	(0.89 : 1.02)	0.13	More symptoms
Reaction Time	0.95	(0.89 : 1.00)	0.07	Slower Reaction
Verbal Fluency	0.93	(0.87 : 1.02)	0.06	Less Word Generation

Logistic regression leveraging clinical and demographic data collected in the acute/sub-acute and 1-year follow up to determine predictors of these long-term imaging changes determined that concussion diagnosis, older age, verbal memory and verbal fluency best predicted the presence of DTI abnormalities 5 years post injury (AUC 0.8 indicating good prediction strength)

Mac Donald, et al, NeuroImage:Clinical 2017

Summary of Findings from the EVOLVE Study

(A prospective, observational, longitudinal research study from point of injury to long term outcome)

- Combat concussion appears to worsen global outcome at 1-year <u>and</u> 5-year follow up.

- Combat Concussion exacerbates symptoms of mental health severity which we observed repeatedly across 4 independent cohorts beyond basic combat exposure.

- Early screening for mental health following acute concussion diagnosis may provide strategic selection for patients who may benefit most from more aggressive treatment to reduce/mitigate long term impact.

- 80% of blast concussion patients sought assistance for mental health issues by 5-year follow up BUT <u>only 19% had sustained resolution</u> of their symptoms.

- New imaging methods have demonstrated abnormalities consistent with brain injury not apparent on conventional MR acquired at the time in theatre, following medical evaluation, at 1-year follow up and at 5-year follow up (with a proportion of blast TBI appearing to have <u>worsening secondary decline</u>).
  - Could this be the earliest evidence of how early head injury exposures may connect to later life neurodegeneration?

- There was an evolution NOT resolution from 1 to 5-year follow up.

- These findings suggest a greater impact of combat-related concussion than previously appreciated and have important clinical implications for aging.

Acknowledgements – A 'small army' of Support

University of Washington
United States

Washington University
United States

PI: David Brody, MD PhD

Dept of Radiology

Marcus Raichle, MD
Josh Shimony, MD PhD
Avi Snyder, MD PhD
Matthew Parsons, MD

Dept of Psychiatry

Elliot Nelson, MD

Dept of Neurology
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Nicole Werner, PhD

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Erik Shumaker, PhD
Elaine Tamez, PhD
Justin Hampton, LCSW
Meghan Jenkins, MSW
Natasha Hilts, MSW
Danielle Marinucci, MSW

Kathryn Stinson, LCSW
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Amanda Hiesele
Laura Daigh
April Reupke
Christine Lakey, LCSW
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Max Tuffy
Morgan Hall
Many Kaur

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Swati Rane, PhD
Serena Bennett
Kris McKown

Dept of Psychiatry
Jesse Fann, MD MPH

Dept of Biostatistics
Nancy Temkin, PhD
Jason Barber, MS

Dept of Rehab Medicine
Sureyya Dikmen, PhD
Carolyn Parsey, PhD

Dept of Pathology
C. Dirk Keene, MD PhD
Caitlin Latimer, MD PhD
Desiree Marshall, MD
Erica Melief, PhD
Lisa Keene
Allison Beller
Kim Howard

Landstuhl Regional Medical Center
Germany
PI: David Zonies, MD

Trauma Surgery & Critical Care

LRMC PI: LTC John Oh, MD (2010-2011)
LRMC PI: COL Raymond Fang, MD (2009 – 2010)
LRMC PI: COL (ret) Stephen Flaherty, MD (2007-2009)
LTC Shawna Scully, MD   Tess Stewart, RN
Kathie Martin, RN   Elizabeth Kassner, RN
Linda Wierzechowski, RN   Caroline Tuman, RN
Yolanda Barnes, RN

Dept of Radiology – MRI Clinic
LTC John Witherow, MD (dec)   TSgt Kris Robertson
Tim Roberts   SSgt Kelly McKay

Kandahar Air Field – Camp Leatherneck
Afghanistan
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CDR Dennis Rivet, MD
LCDR Maria Barefield, OT
LCDR Josh Duckworth, MD
CDR Dean Asher, MD
LCDR Benjamin Drinkwine, MD
LCDR Don Labarge, MD
CDR, Todd May, DO
LTC, John Ritter, MD

Thank You to all men and women of the US Armed Forces and those that provide care for the wounded.

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