Brain Injury and Psychological Health following Combat Deployment: Implications for long term outcome

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Poll Question

- What is your association to VA Health System?
  - Student, Trainee, or Fellow
  - Clinician
  - Researcher
  - Administrator
  - Other

Disclosure: No Apparent Conflicts of Interest

- Funding for this research was provided by:
  - NIH RO1 - Evaluation Of Longitudinal outcomes in mild TBI Active-Duty Military and Veterans – The EVOLVE Study (PI: C. Mac Donald)
  - DoD-CENC -Assessment of long term outcome & Disability in Active-duty military Prospectively examined following concussive TBI: 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) 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 and now 5 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 VA care following service separation.

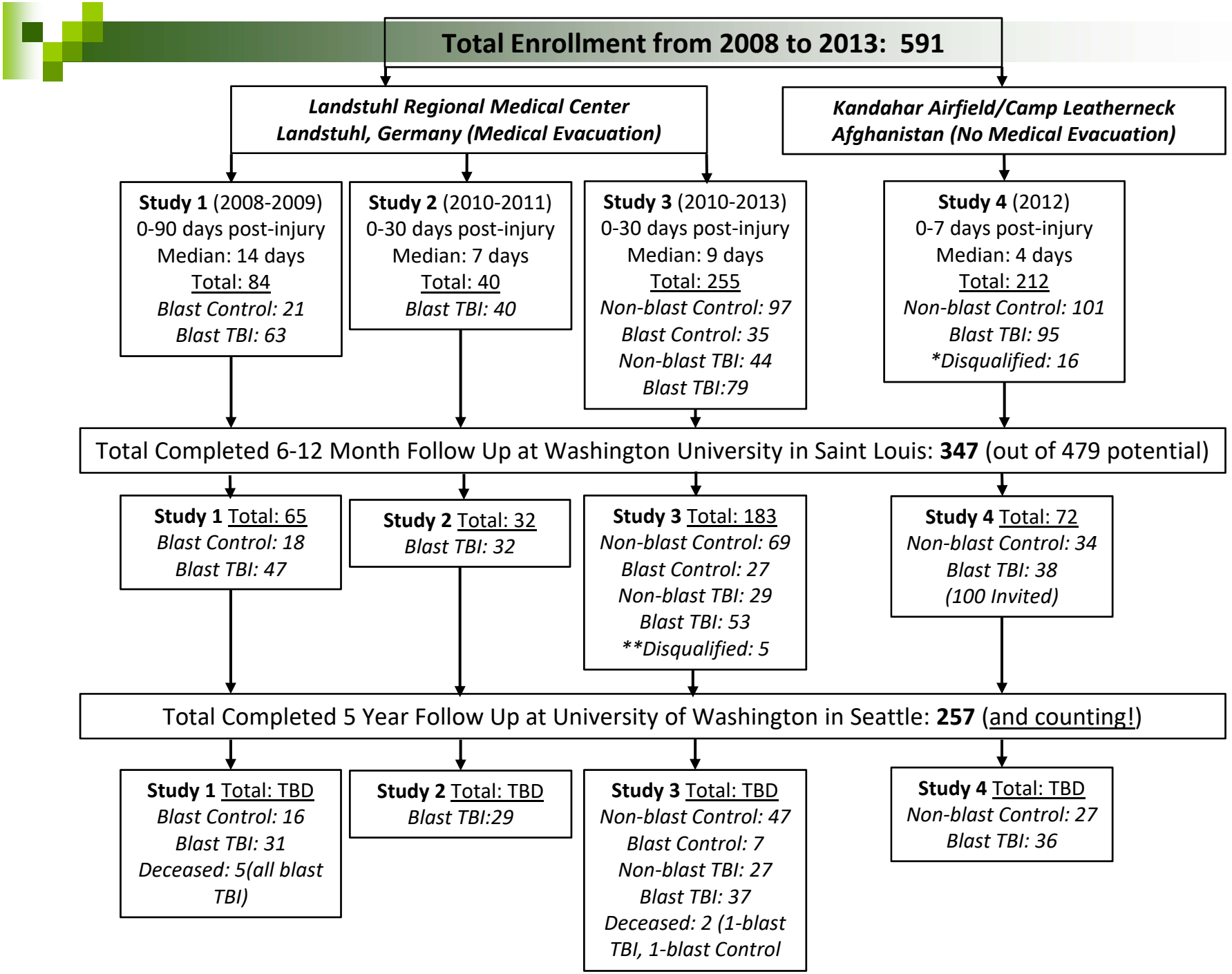
Study Objectives

- **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 5-7 year 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.

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.
  - **ALL SUBJECTS MET THE DOD DEFINITION FOR MILD UNCOMPLICATED BRAIN INJURY**
- *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 6-12 Month Follow Up at Washington University in Saint Louis: 347 (out of 479 potential)
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: 257 (and counting!)
Study 1 Total: TBD
Blast Control: 16
Blast TBI: 31
Deceased: 5(all blast TBI)
Study 2 Total: TBD
Blast TBI:29
Study 3 Total: TBD
Non-blast Control: 47
Blast Control: 7
Non-blast TBI: 27
Blast TBI: 37
Deceased: 2 (1-blast TBI, 1-blast Control
Study 4 Total: TBD
Non-blast Control: 27
Blast TBI: 36

Part 1

Findings from in-theatre evaluation of non-medically evacuated blast TBI service members

Neurology. 2015 Jul 21;85(3):219-27

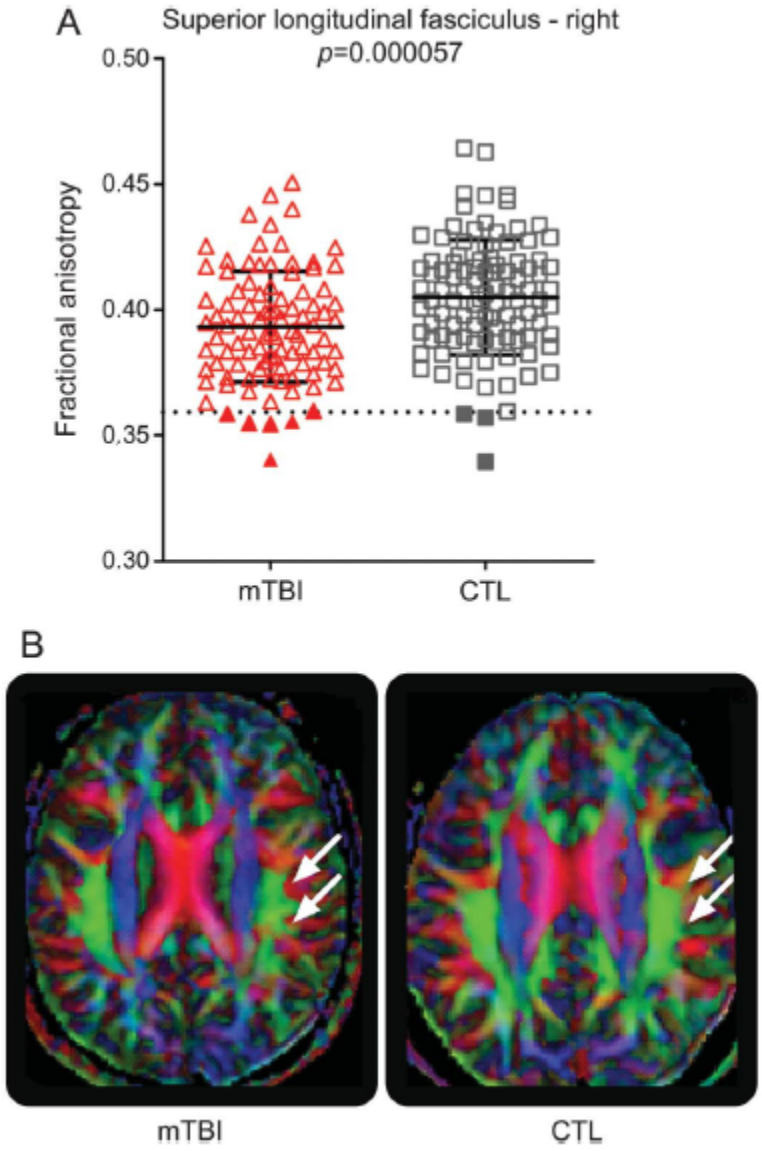
Clinical and imaging assessment of acute combat mild traumatic brain injury in Afghanistan

Octavian Adam, MD*
Christine L. Mac Donald, PhD*
Dennis Rivet, MD
John Ritter, MD
Todd May, DO
Maria Barefield, OTD
Josh Duckworth, MD
Donald LaBarge, MD
Dean Asher, MD
Benjamin Drinkwine, MD
Yvette Woods, PhD
Michael Connor, PsyD
David L. Brody, MD, PhD

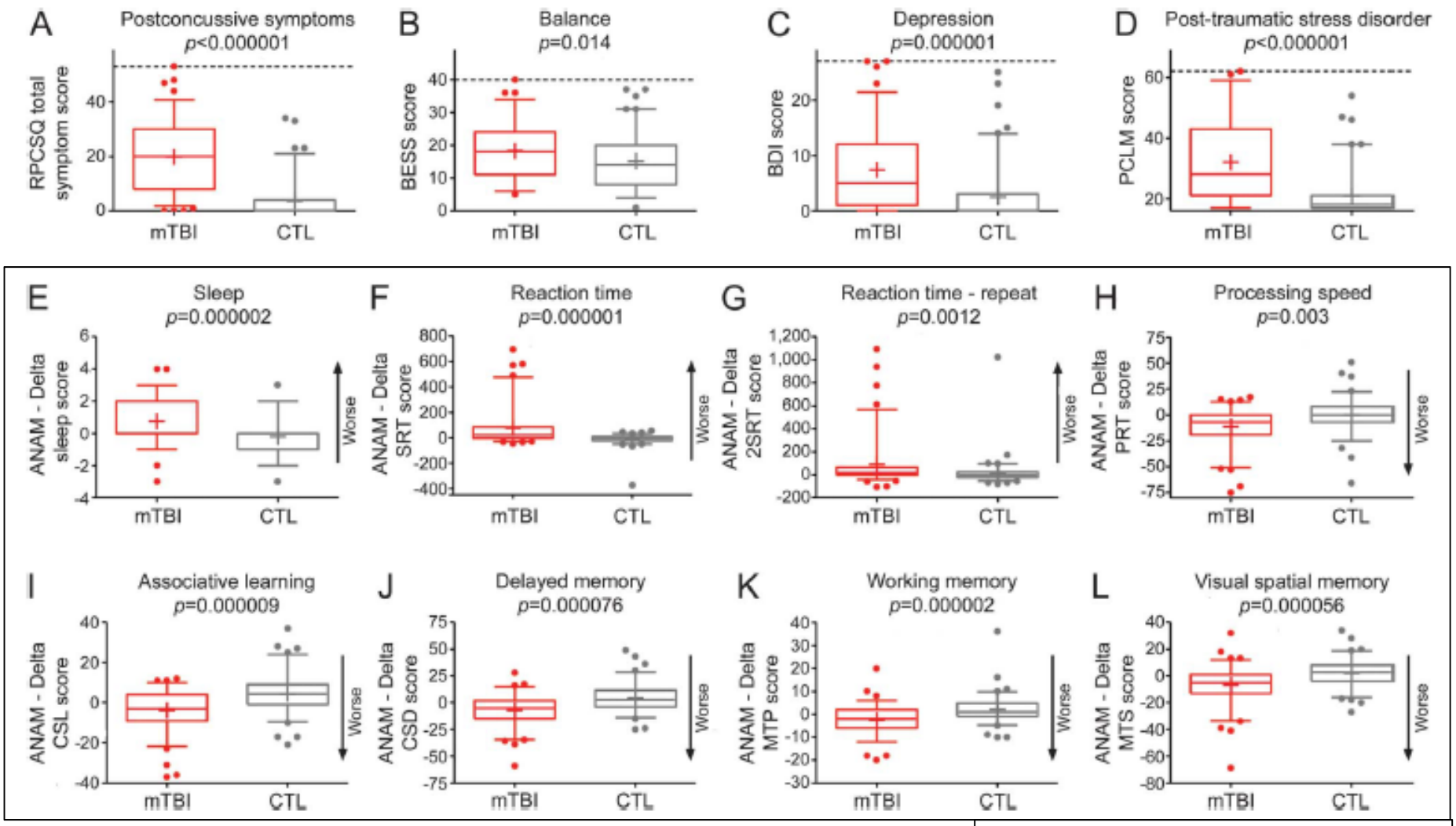
Imaging Findings from Kandahar Airfield and Camp Leatherneck in Afghanistan

- Conventional imaging collected in Afghanistan was unremarkable for evidence of pathanatomic lesions consistent with brain injury
- Advanced neuroimaging collected at the same time did reveal abnormalities as shown in this figure in line with previous reports suggestive of axonal disruption.
- This data was collected using diffusion tensor imaging, a quantitative MRI method most commonly used to measure white matter integrity
- NOTE: MRI scanners are not created equal and it should be appreciated that likely with more modern technology, findings such as reductions in Fractional anisotropy may be more pronounced.

Adam, Mac Donald, et al Neurology, 2015



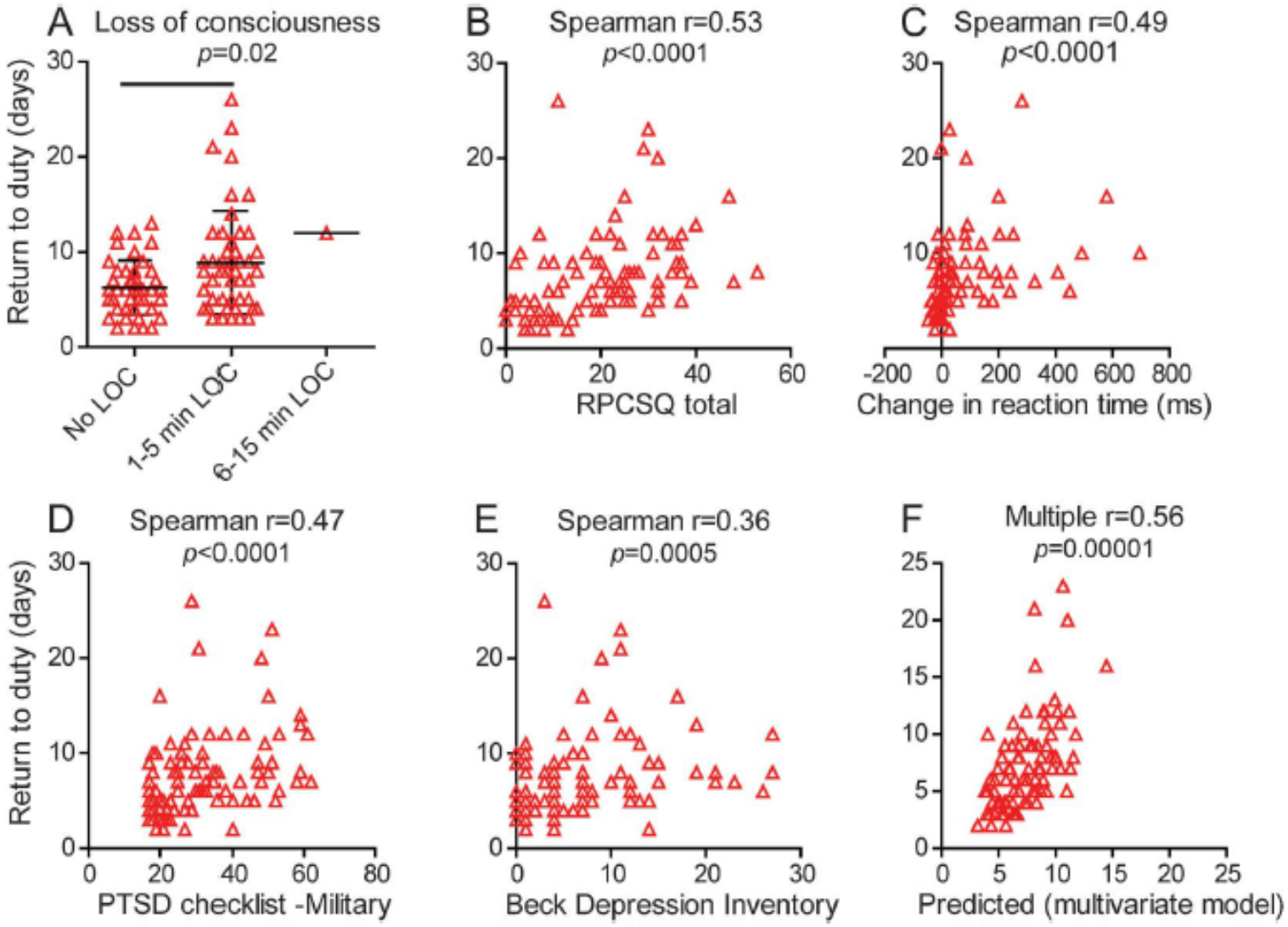
Clinical Assessment Measures (0-7 days)



Adam, Mac Donald, et al Neurology, 2015

Compared to Pre-Deployment Baseline

Clinical Correlates of Return to Duty



Adam, Mac Donald, et al Neurology, 2015

Part 1 Summary – In Theatre Findings

- Evaluation 0-7 days post injury in blast concussion patients revealed more severe symptoms of depression and post traumatic stress, in addition to post concussive symptoms, impaired balance, and cognitive dysfunction identified on the ANAM in comparison to pre-deployment baseline testing.
  - NOTE: No significant differences in baseline ANAM comparing control to concussion.
- While blast concussion patients with LoC vs AoC did take slightly longer to return to duty much stronger correlates with RTD where post-concussive symptoms, symptoms of depression and post traumatic stress, and reaction time on ANAM.
- Advanced neuroimaging collected in theatre did reveal areas of abnormality consistent with injury that were not appreciated on the conventional imaging acquired at the same time.
- **QUESTION**: How will these patients look at ~1 year follow up when the civilian literature suggest the majority should make full recovery?

Part 2

Findings from ~1 year follow up in non-medically evacuated blast concussion who were treated in theater and returned to duty

Brain Advance Access published March 4, 2015

doi:10.1093/brain/awv038 BRAIN 2015: Page 1 of 13 | 1

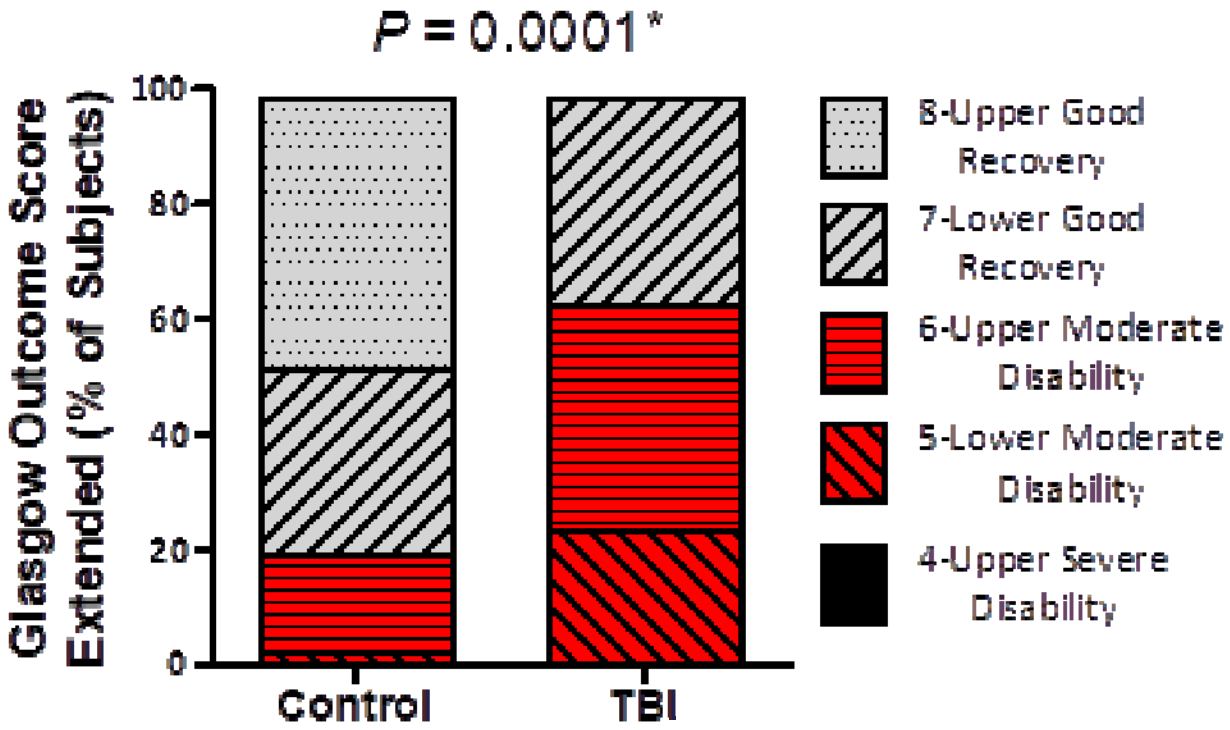
BRAIN
A JOURNAL OF NEUROLOGY

Acute post-traumatic stress symptoms and age predict outcome in military blast concussion

Christine L. Mac Donald,[1,†,*] Octavian R. Adam,[2,#,*] Ann M. Johnson,[1] Elliot C. Nelson,[1] Nicole J. Werner,[1] Dennis J. Rivet[2,$] and David L. Brody[1]

*These authors contributed equally to this work.

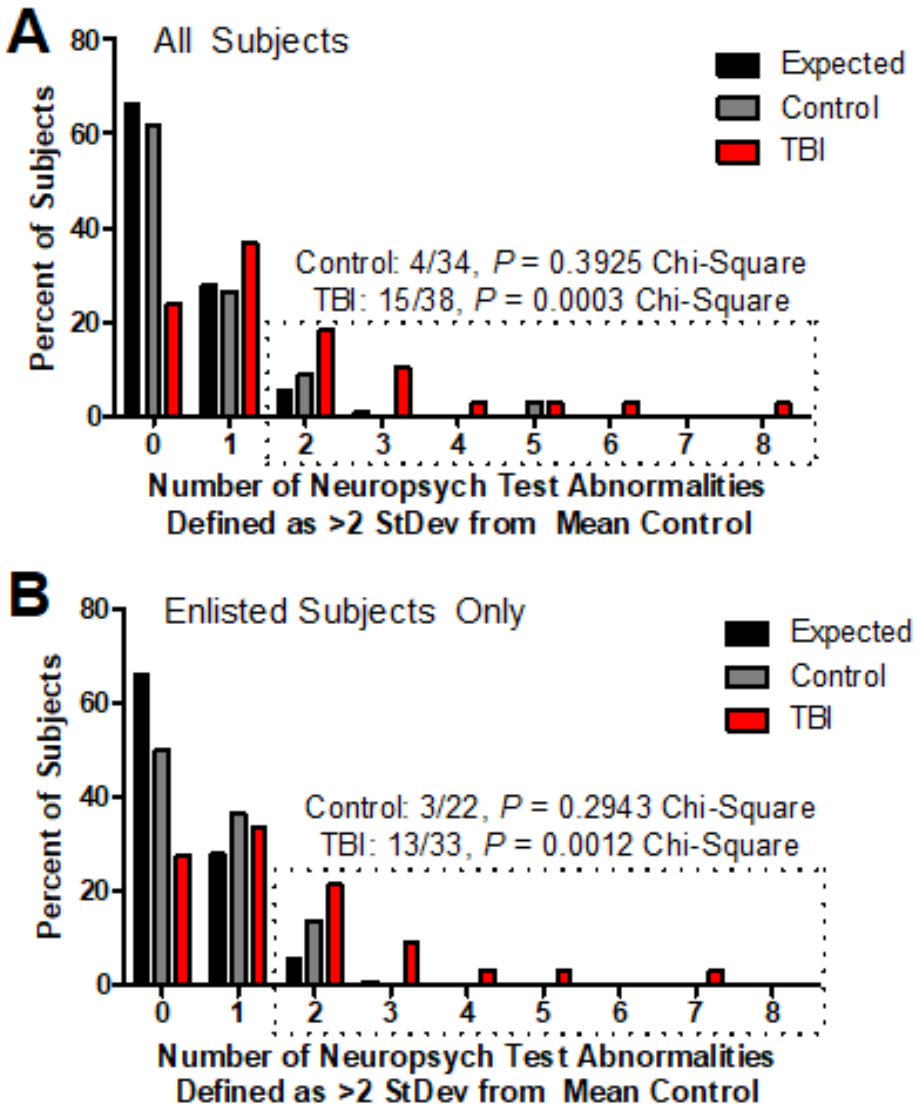
Global Disability



Global Measure of Outcome ~1 year after enrollment indicate worse outcomes in concussive blast TBI patients treated in theatre vs. combat deployed Controls

Mac Donald, Adam, et al Brain, 2015

Cognitive Performance



Mac Donald, Adam, et al Brain, 2015

Larger Numbers of Concussive blast TBI Service Members than Controls were found to have 2 or more Neuropsychological Performance Abnormalities at ~1 year Follow Up

NOTE: There were no significant differences in cognitive performance at the group level on any of the 10 cognitive test measures. Only this secondary analysis revealed a subset of Concussive blast TBI service members with lasting deficits.

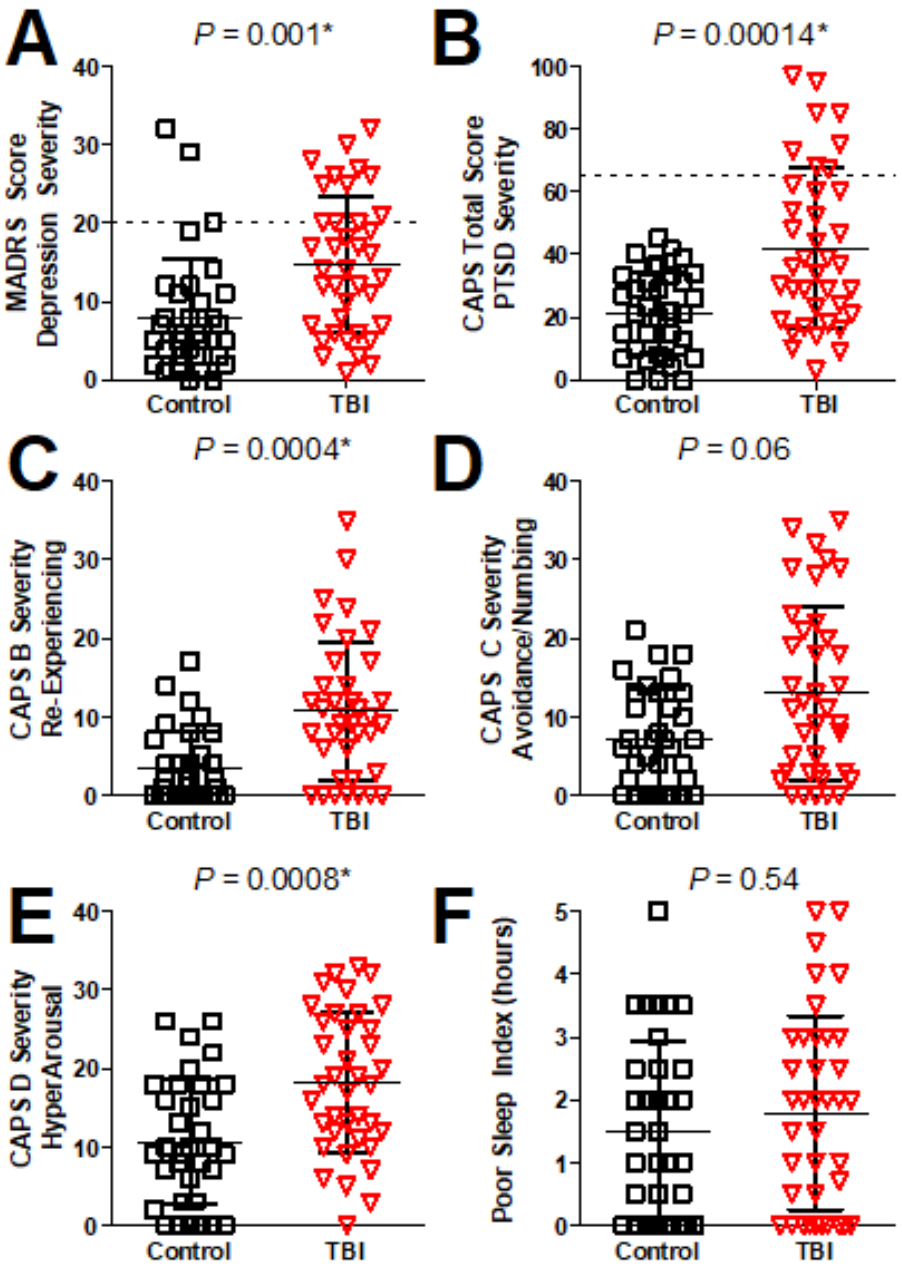
Mental Health

Symptoms of Depression (A) and Post Traumatic Stress (B) were significantly elevated in Concussive blast TBI service members treated in theatre at ~1-year follow up in comparison to combat deployed controls.

No different in sleep impairment (F)

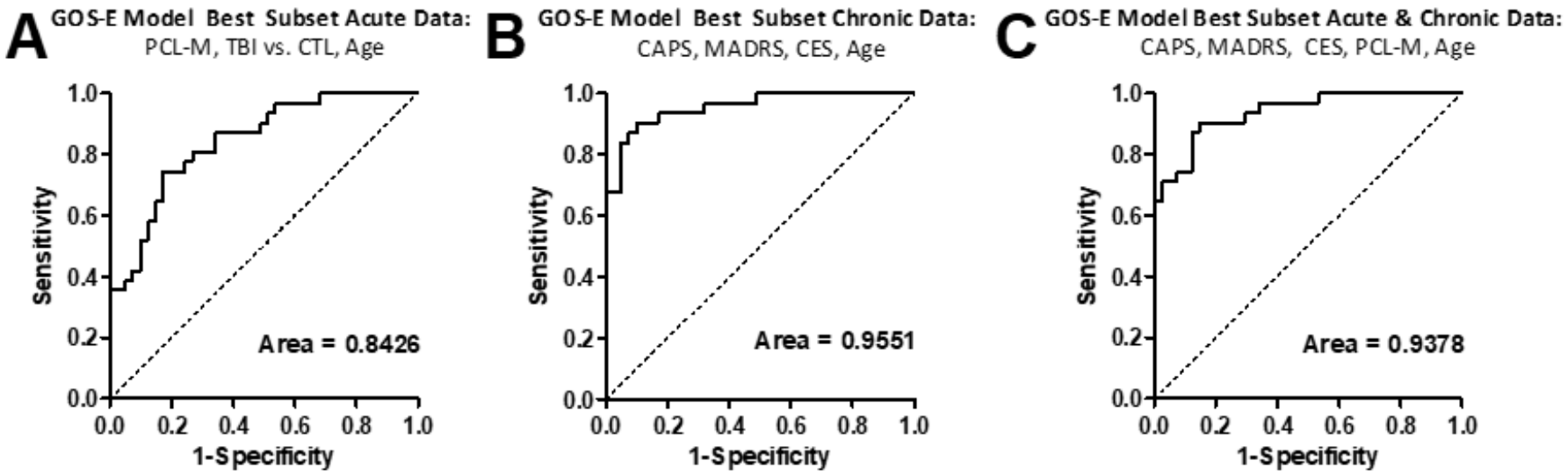
Of note, post traumatic stress domains of re-experiencing/reliving (C) and hyperarousal/hypervigilance (E) were particularly affected.

Dotted lines on panels A & B indicate clinical cutoff for moderate/severe symptoms



Mac Donald, Adam, et al Brain, 2015

Predictors of Poor Outcome



Considering all measures at each time point including assessments for cognitive performance, post concussive symptoms, mental health symptoms, combat intensity exposure, number of deployments, number of prior concussions (TBI group only) and patient demographics the top models at each time point largely included measures of mental health that best predicted poor outcome as evidenced by the GOSE a measure of global disability.

Mac Donald, Adam, et al Brain, 2015

Part 2 Summary –In-Theatre to ~1 year outcome comparison in Blast Concussion

- Concussive blast TBI service members treated in theatre faired quite poorly at ~1 year outcome in comparison to combat deployed controls on measures of global disability, mental health symptoms, and a subset were observed to have lasting cognitive deficits.
- Predictors of poor ~ 1 year outcome from data collected in theatre included severity of post traumatic stress (PCL-M), diagnosis of concussion, and older age. None of the cognitive performance measures, time to return to duty from injury, history of concussion, or previous blast exposure history, etc contributed to the top model.
- Surprisingly, a considerable number of non-medically evacuated Concussive blast service members did not completely recover ~1 year post-injury.
- **QUESTION**: How will these patients compare to service members who required Medical Evacuation following Concussive blast TBI?

Part 3

Findings from evaluation of medically evacuated blast TBI service members

Part 3 A – Imaging Findings in Medically Evacuated Blast Concussion

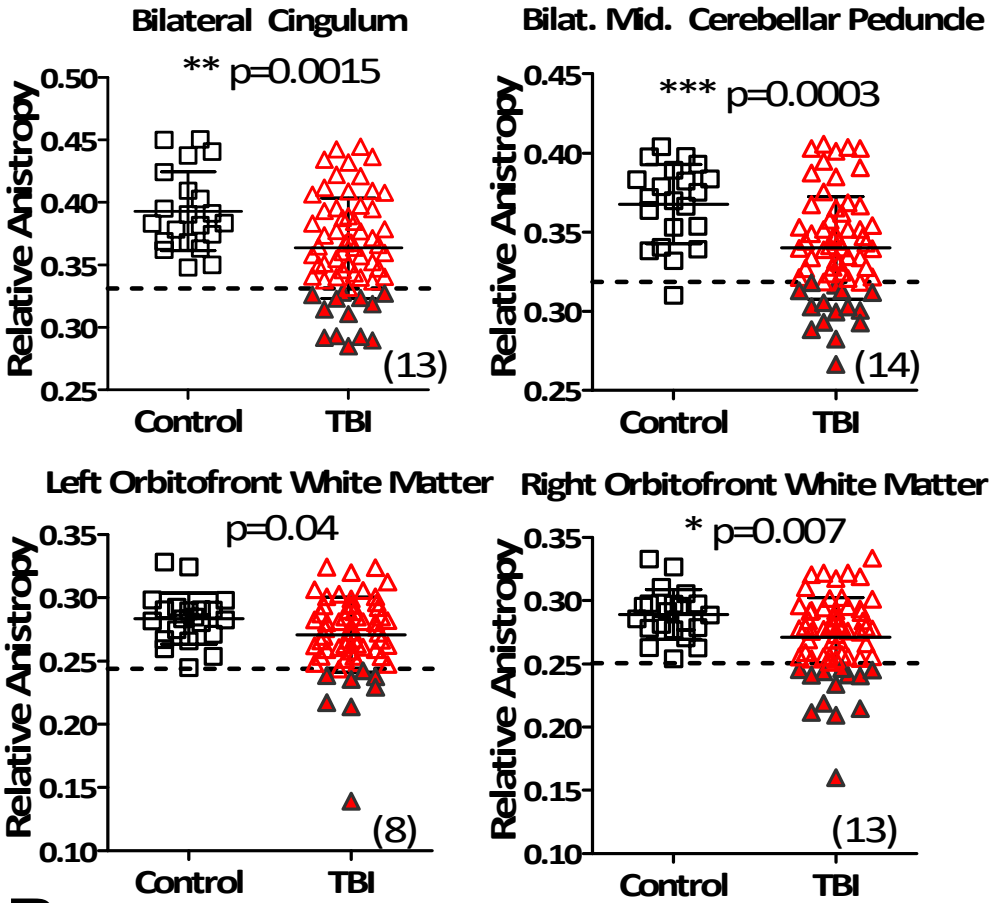
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 2, 2011 VOL. 364 NO. 22

Detection of Blast-Related Traumatic Brain Injury in U.S. Military Personnel

Christine L. Mac Donald, Ph.D., Ann M. Johnson, Dana Cooper, B.S., Elliot C. Nelson, M.D., Nicole J. Werner, Ph.D., Joshua S. Shimony, M.D., Ph.D., Abraham Z. Snyder, M.D., Ph.D., Marcus E. Raichle, M.D., John R. Witherow, M.D.,* Raymond Fang, M.D., Stephen F. Flaherty, M.D., and David L. Brody, M.D., Ph.D.

Imaging Findings from Landstuhl Regional Medical Center, Germany

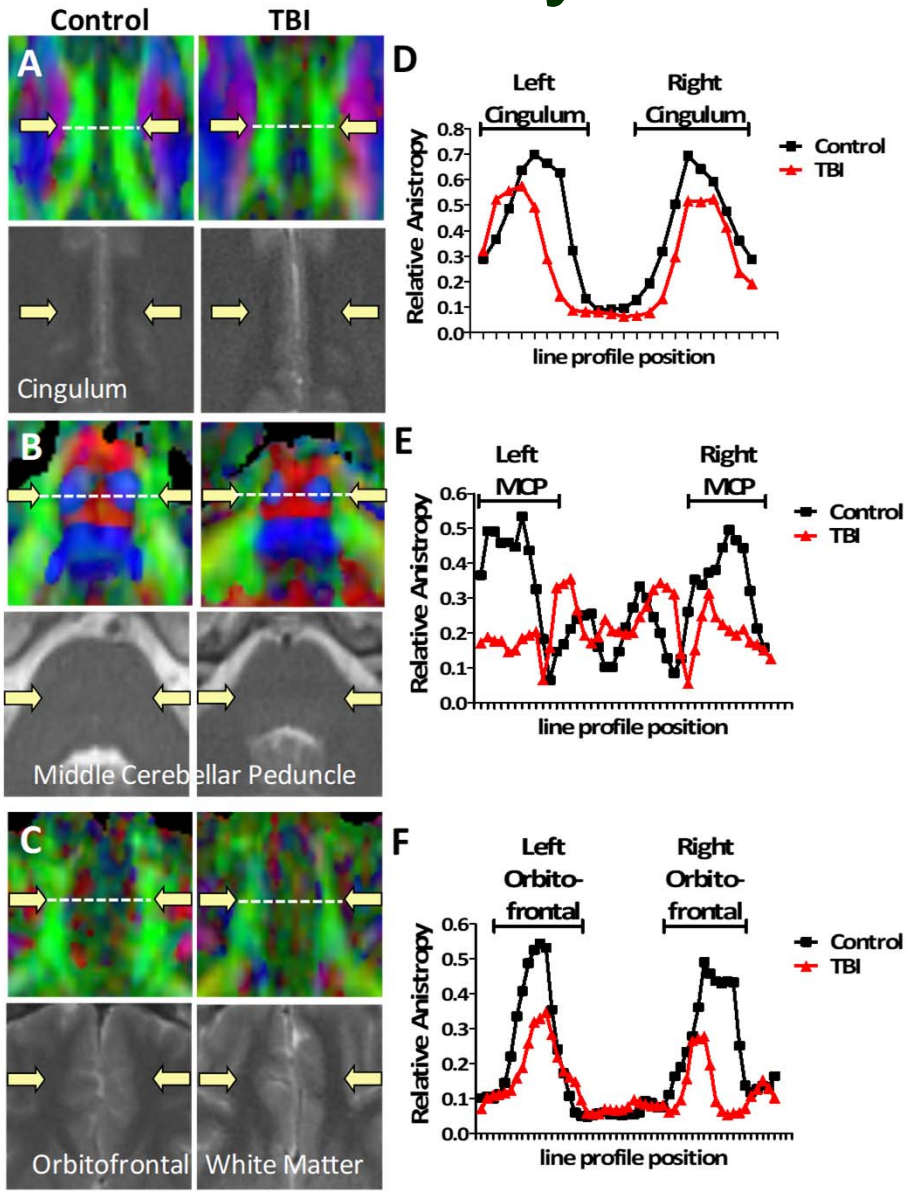


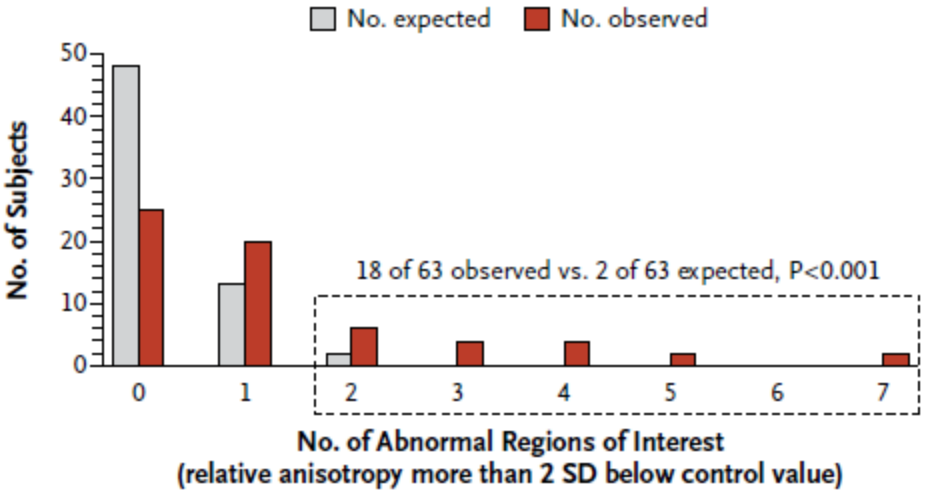
Conventional imaging collected in Germany was unremarkable for evidence of pathanatomic lesions consistent with brain injury.

In contrast, Diffusion Tensor Imaging identified a variety of regions of abnormality consistent with white matter injury.

Mac Donald et al, NEJM 2011

Sensitivity on the 'Per Patient' Level



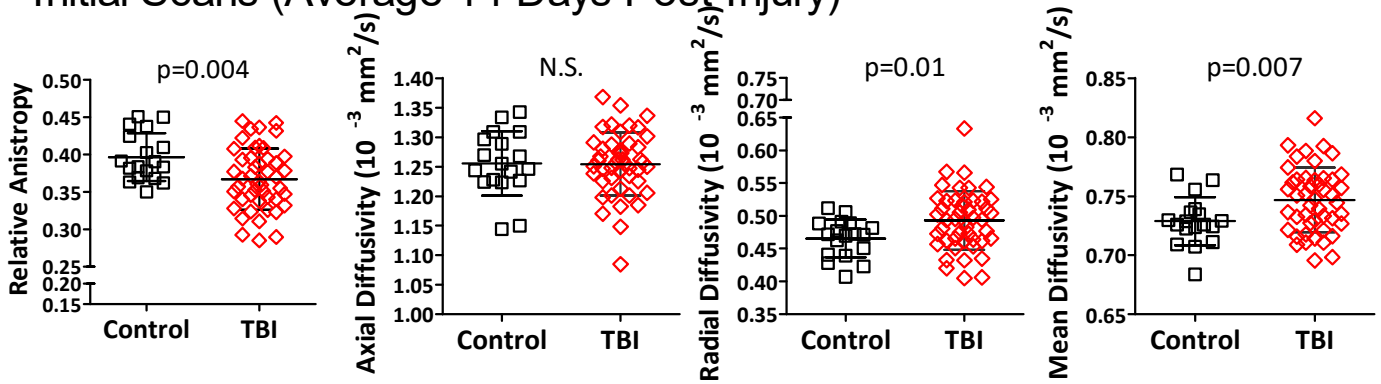


Results are useful even on a single subject level providing support for the clinical relevance of this quantitative imaging method.

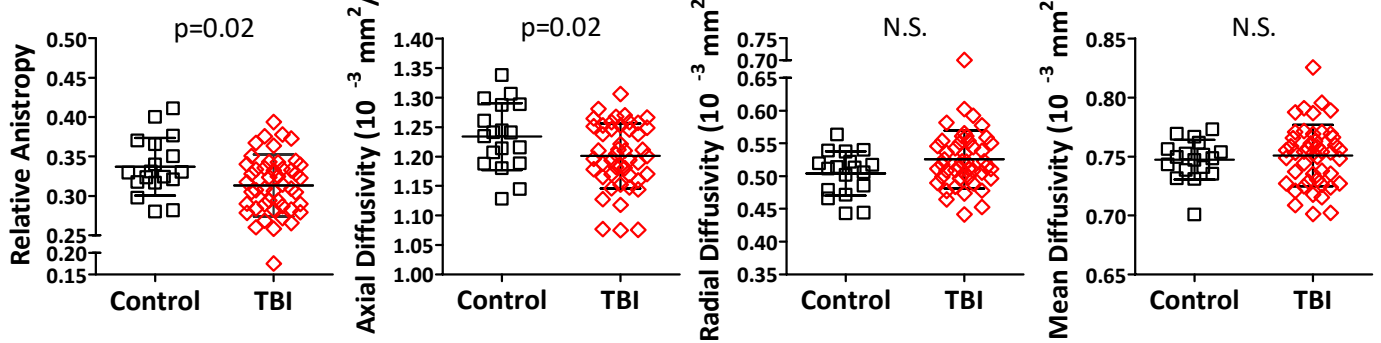
Mac Donald et al, NEJM 2011

Follow-up Scans ~1 Year Post injury: 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, NEJM 2011

Part 3 B – Clinical Outcome Findings in Medically Evacuated Blast Concussion

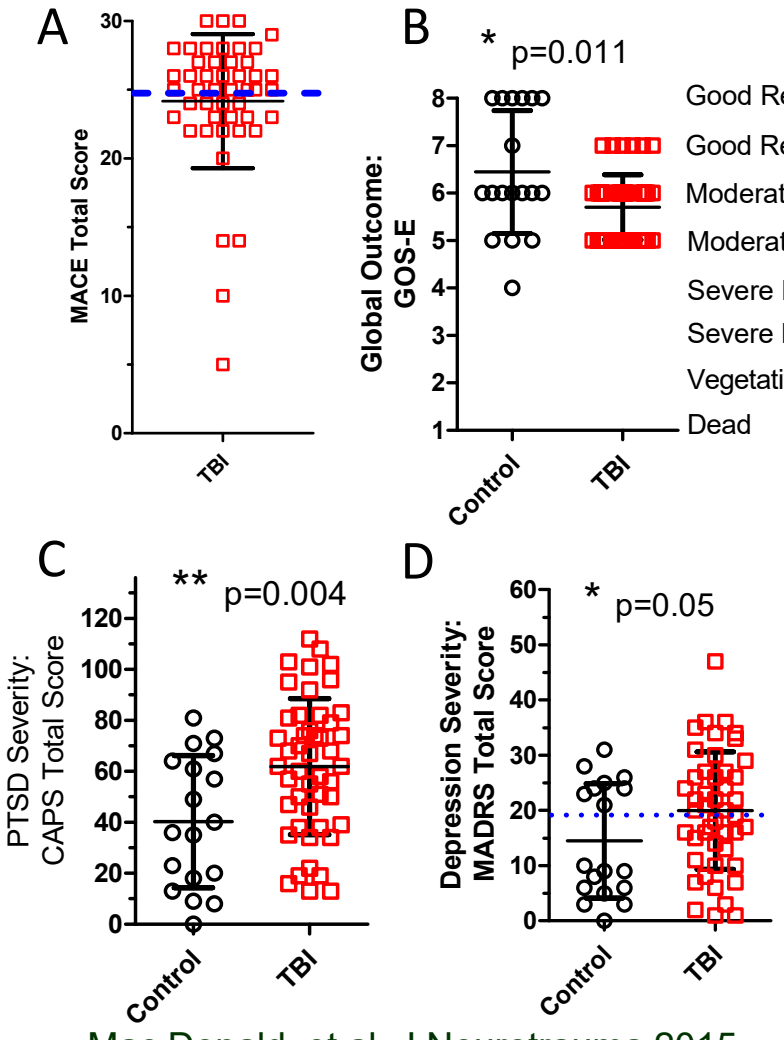
JOURNAL OF NEUROTRAUMA 31: 1–10 (XXXX 00, 2014)

DOI: 10.1089/neu.2013.3173

Functional Status after Blast-Plus-Impact Complex Concussive Traumatic Brain Injury in Evacuated United States Military Personnel

Christine L. MacDonald,[1] Ann M. Johnson,[1] Elliot C. Nelson,[1] Nicole J. Werner,[1] Col. Raymond Fang,[2,3] Col. (ret) Stephen F. Flaherty,[2,4] and David L. Brody[1]

Concussion Severity in Germany and Significant Findings at ~1year outcome



Mac Donald, et al, J Neurotrauma 2015

While the majority of medically evacuated Concussive blast patients were above the threshold for 'symptomatic concussion' in the ~2 week sub-acute phase in Germany, a significant number faired poorly at ~1-year follow up with symptoms of post traumatic stress and depression being the most discriminating between groups. Comparison of cognitive testing across groups on 10 different measures was normal.

QUESTION: Is this unique to blasted-related concussion sustained in combat?

Research

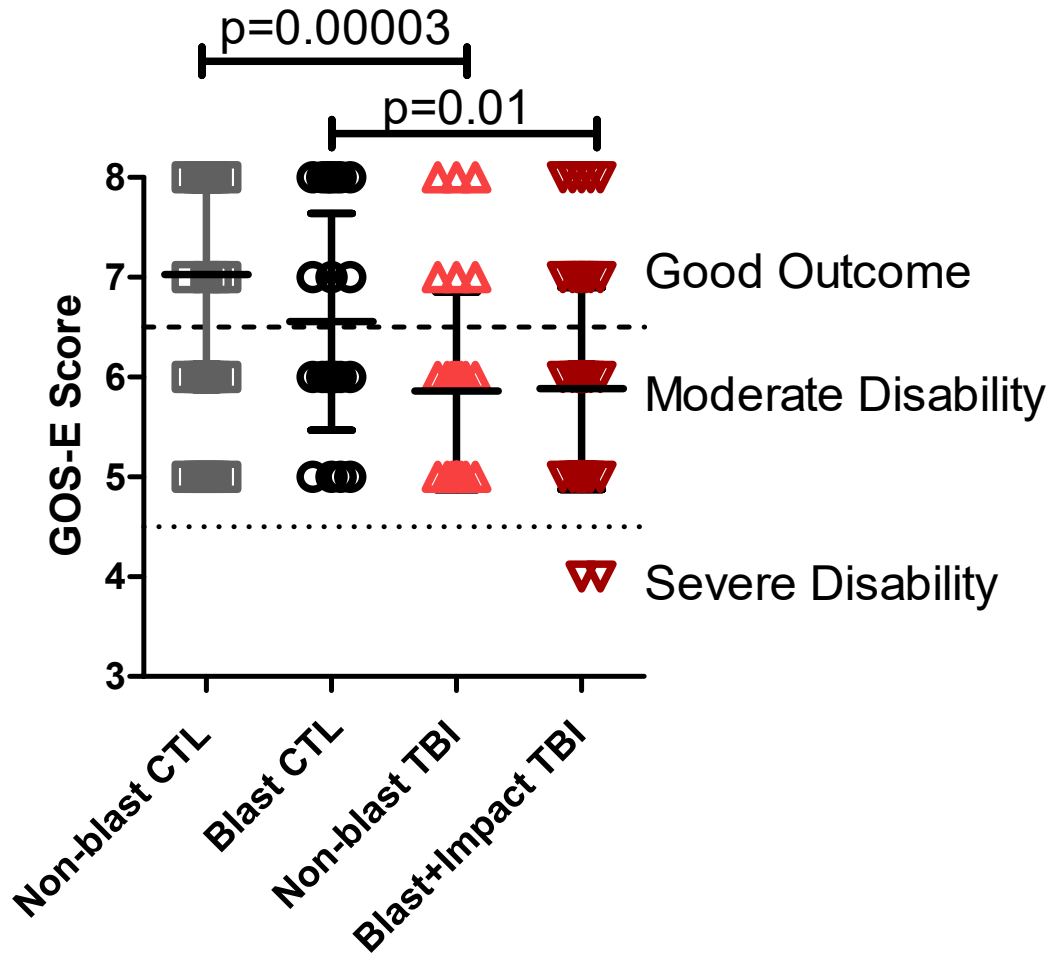
JAMA Neurology | Original Investigation

Prospectively Assessed Clinical Outcomes in Concussive Blast vs Nonblast Traumatic Brain Injury Among Evacuated US Military Personnel

Christine L. Mac Donald, PhD; Ann M. Johnson; Linda Wierzechowski, RN; Elizabeth Kassner, RN; Theresa Stewart, RN; Elliot C. Nelson, MD; Nicole J. Werner, PhD; David Zonies, MD, MPH; John Oh, MD; Raymond Fang, MD; David L. Brody, MD, PhD

JAMA Neurol. doi:10.1001/jamaneurol.2014.1114
Published online June 16, 2014.

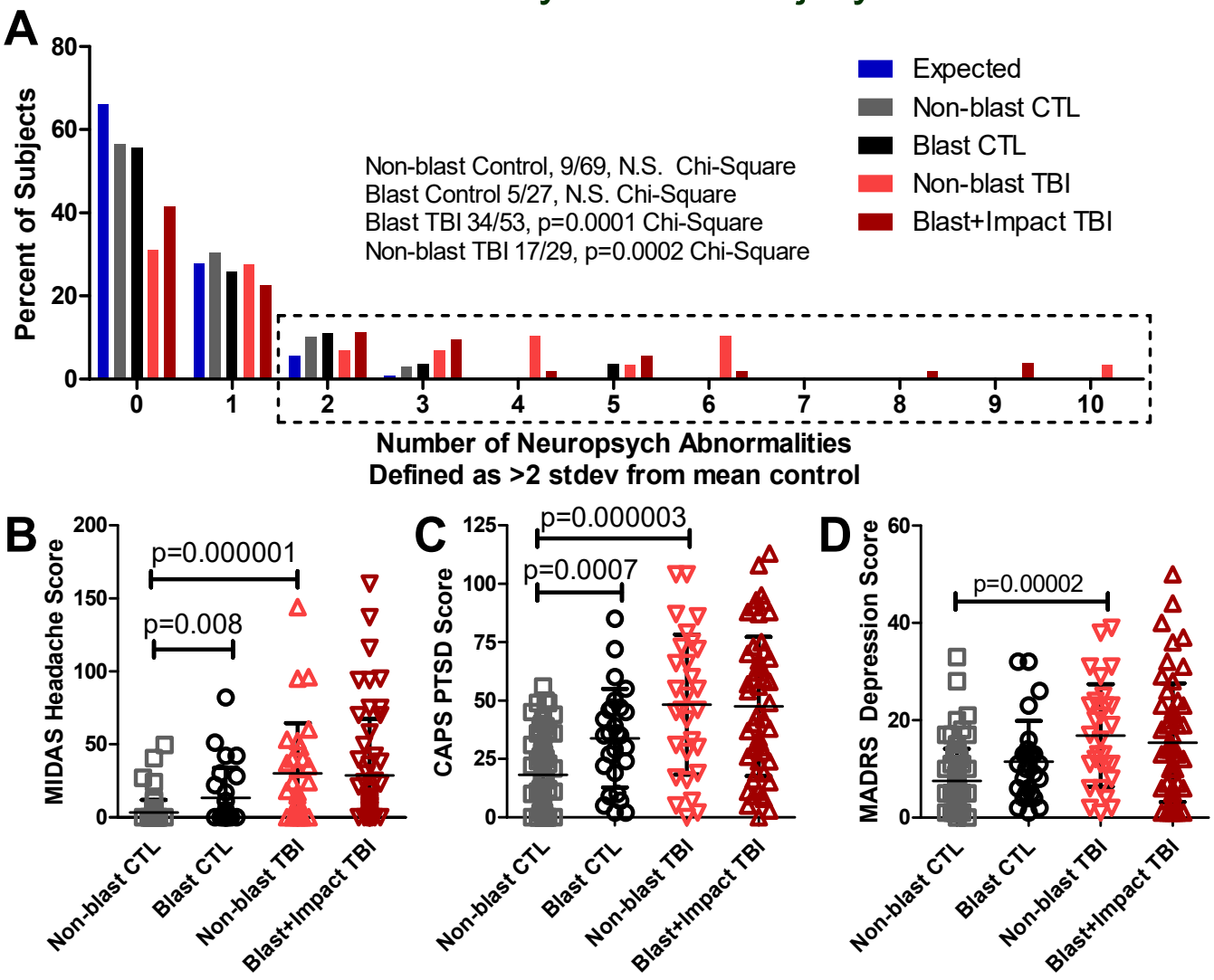
Global Disability following blast vs non-blast combat concussion



- No difference in overall outcome comparing blast vs. non-blast combat concussion ~1 year post–injury
- Significant differences in global disability were observed comparing blast AND non-blast combat concussion to combat deployed controls

Mac Donald, et al, JAMA Neurology 2014

Clinical Outcomes ~1 year Post-Injury: Blast vs. Non-Blast Concussion



Mac Donald, et al, JAMA Neurology 2014

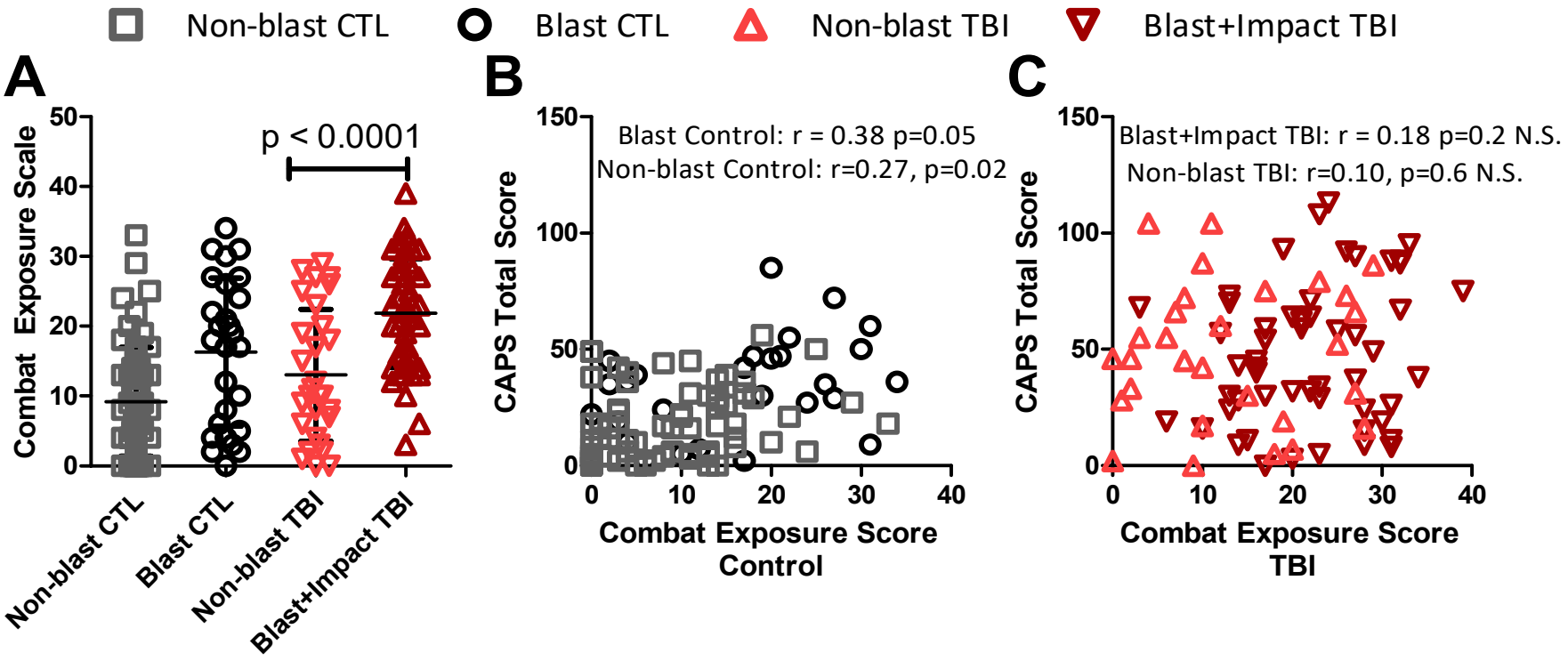
Again, cognitive performance was normal at the group level while subsets of both blast and non-blast combat concussion patients were observed to have sustained deficits.

BOTH blast and non-blast combat concussion service members exhibited significantly greater headache impairment, post-traumatic stress and depression severity ~1 year post-injury compared to combat deployed controls

NO differences in clinical outcomes were observed between blast and non-blast combat concussion

Interestingly, there was a difference on some measures comparing blast exposed to non-blast exposed controls

Relationship of PSTD to Intensity of Combat Exposure



Take home message:

1. **The relationship between combat exposure and PTSD severity is differentially related in Combat concussion compared to Controls.**

2. **In the presence of combat concussion, '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

Part 3 Summary –Medically evacuated blast and non-blast concussion: Comparison to ~1 year outcome

- Diffusion Tensor Imaging identified a variety of regions of abnormality consistent with white matter injury at both the sub-acute (2 week) and ~1 year time points that appear to evolve not resolve over time.

- Both blast and non-blast combat concussion patients faired poorly at ~1 year outcome on overall disability, symptoms of post traumatic stress, depression, headache, and neurobehavior while cognitive deficits were largely resolved with the exception of a subset of patients.

- Combat intensity exposure did NOT correlate with severity of post traumatic stress in either combat concussion group while correlations were observed in combat deployed controls.

- **QUESTION**: Are there differences in clinical outcomes comparing medically evacuated to non-medically evacuated combat concussion patients?

Part 4

Comparison in Clinical Outcomes Medically Evacuated vs. Non-Medically Evacuated Combat Concussion

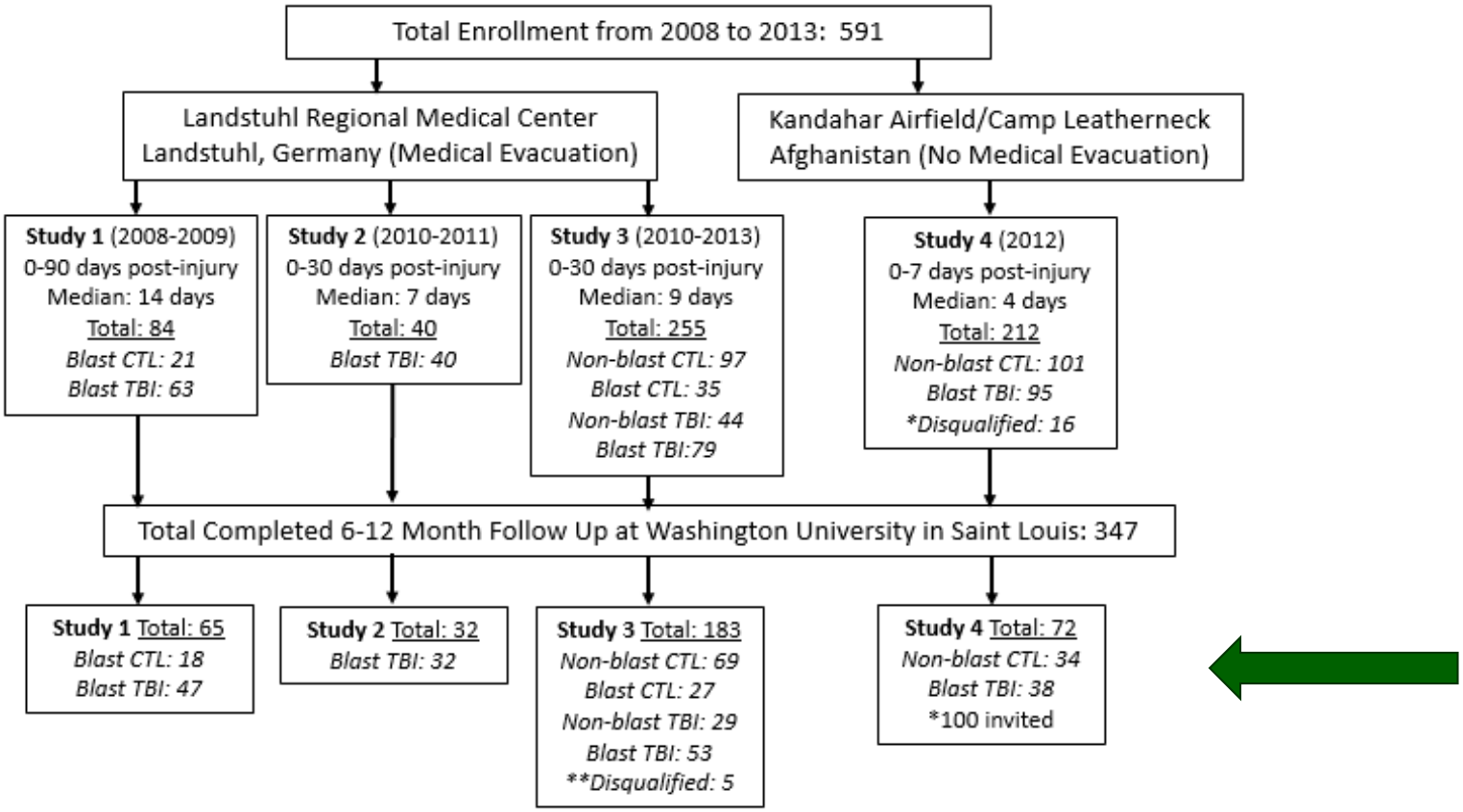
JOURNAL OF NEUROTRAUMA 33:1–14 (XXXX 00, 2016)

DOI: 10.1089/neu.2016.4434

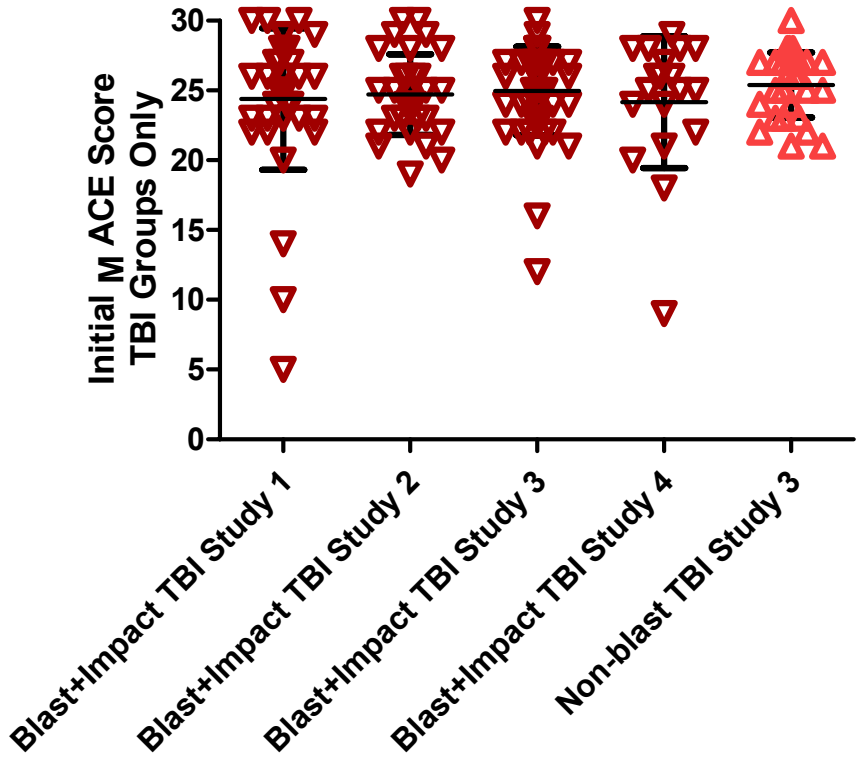
Original Article

Outcome Trends after US Military Concussive Traumatic Brain Injury

Christine L. Mac Donald,[1,2] Ann M. Johnson,[1] Linda Wierzechowski,[3] Elizabeth Kassner,[3] Theresa Stewart,[3] Elliot C. Nelson,[1] Nicole J. Werner,[1] Octavian R. Adam,[4,5] Dennis J. Rivet,[4,6] Col. Stephen F. Flaherty,[3,7] Lt. Col. John S. Oh,[3,8] Lt. Col. David Zonies,[3,9] Col. Raymond Fang,[3,10] and David L. Brody[1]



Concussion Severity – Systematic Injury Severity



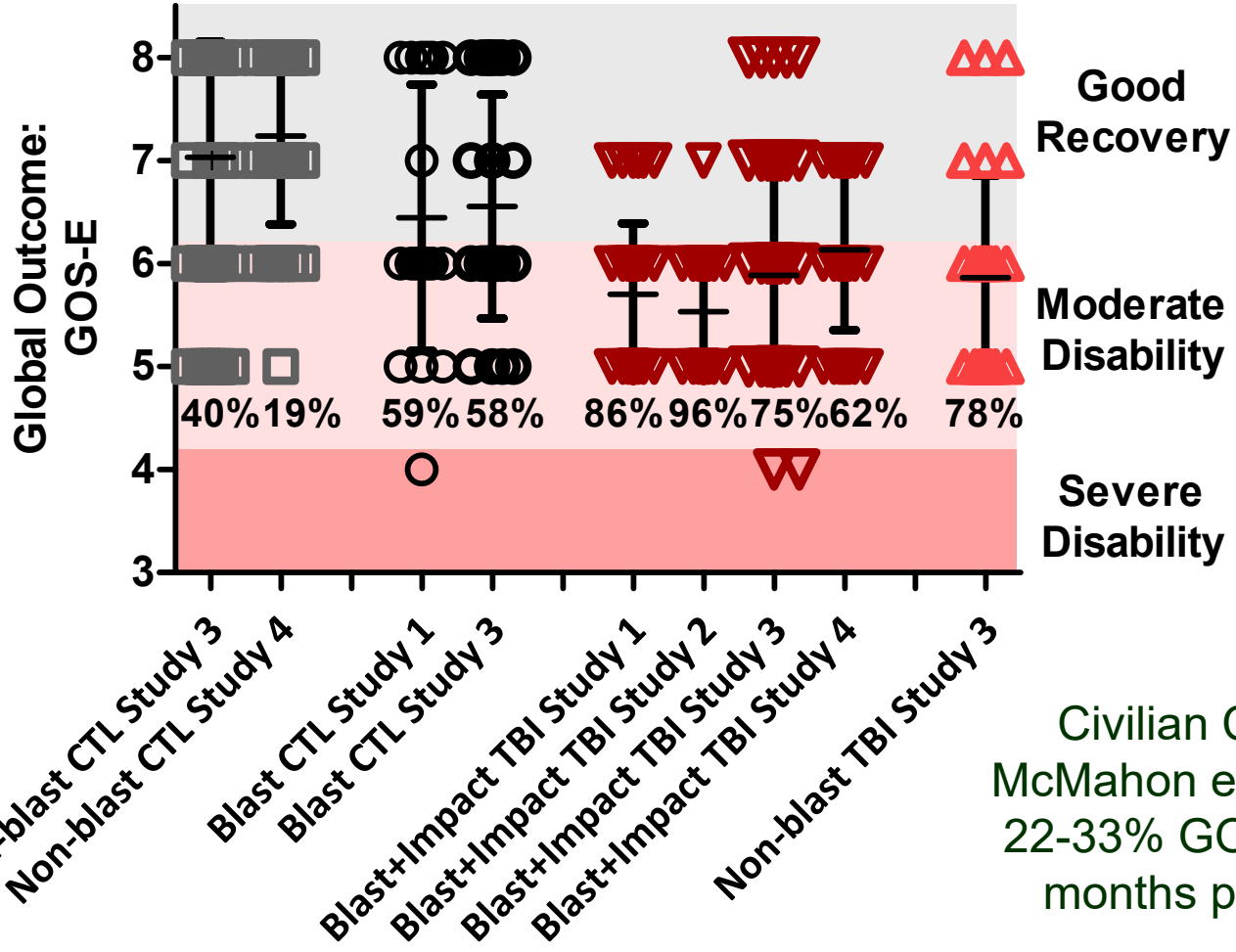
Study	% of Patients ISS Score > 0	ISS Mean	ISS Stdev
Study 1 & 2	22.62	11.16	7.57
Study 3	13.94	5.46	4.22
Study 4	0	0	0

No significant differences in Concussion Symptom Severity between med-evac and non-med-evac combat concussion patients across groups on the Military Acute Concussion Evaluation (MACE)

Significant differences in systemic injury severity measured by ISS were observed across groups

Mac Donald, et al, J Neurotrauma 2016

Global Disability at ~1 Year Post-Injury



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**

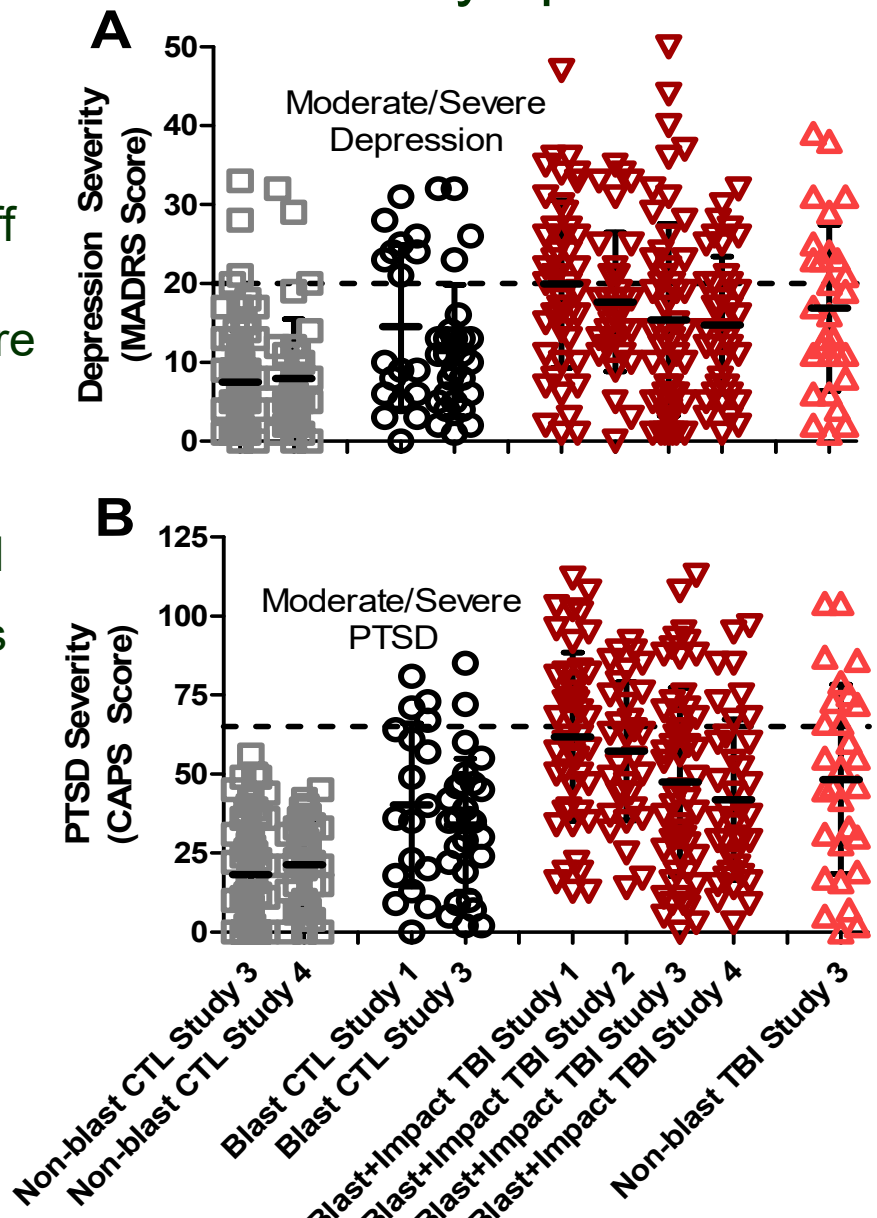
Mac Donald, et al, J Neurotrauma 2016

Depression & PTSD Symptoms at ~1 year Post-Injury

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

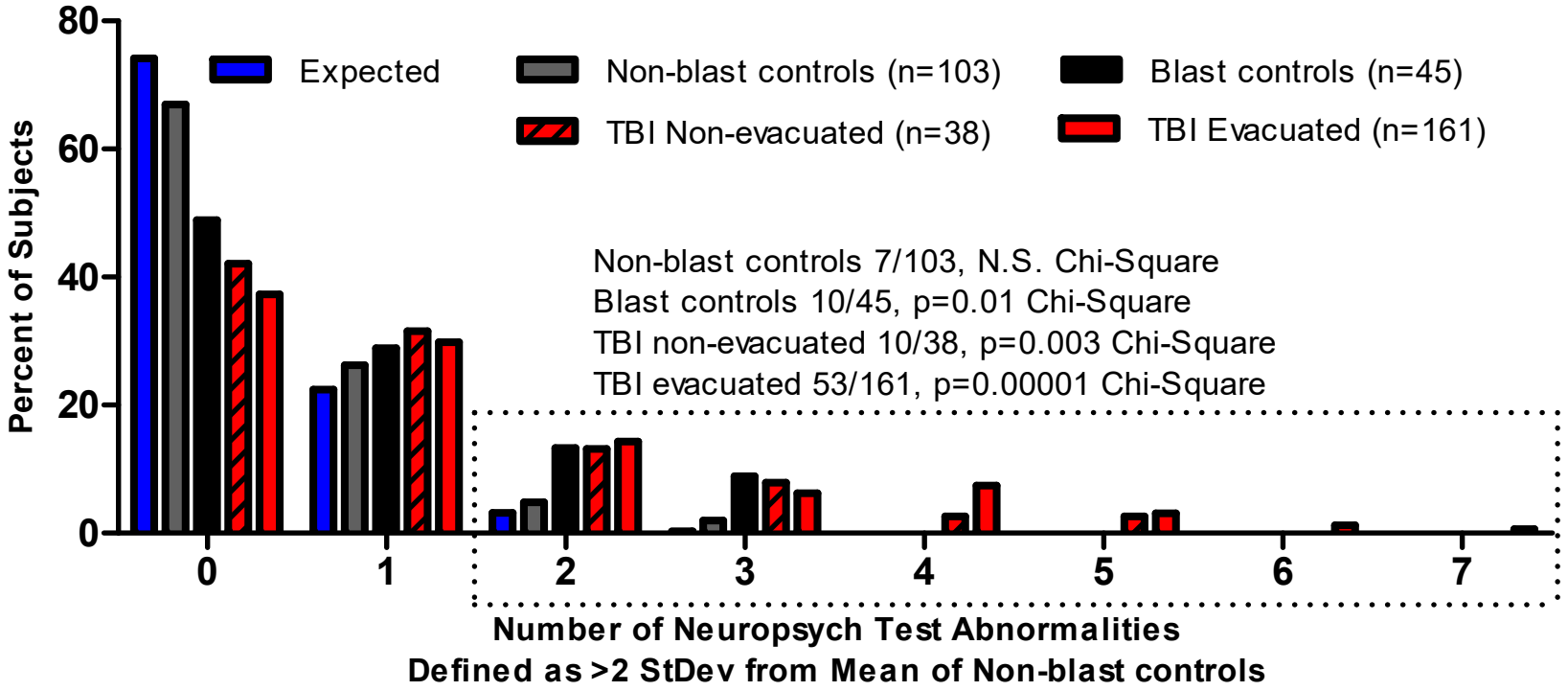
2. No distinction between Blast & Non-blast TBI

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 2016

Cognitive Performance ~1 year Post-Injury



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

Part 4 Summary –Medically evacuated vs. Non-Medically Evacuated: Comparison of ~1 year outcome

- The clinical presentation of medically evacuated and non-medically evacuated combat concussion patients was indistinguishable at ~1 year outcome.

- Repeated across 4 distinct cohorts, all combat concussion groups, blast/non-blast and med-evac/non-med-evac faired quite poorly at ~1 year outcome on measures of global disability, neurobehavior, symptoms of mental health, headache impairment while at the group level cognitive performance was relatively normal compared to combat deployed controls.

- Interestingly, across 2 distinct cohorts, blast exposed control participants were found to also fair significantly more poorly than non-blast exposed controls suggesting a 'sub-concussive' impact of exposure on outcome.

- **QUESTION**: Do these findings resolve at longer term outcome?

Part 5

Initial findings from ~5-7 year outcome compared to earlier evaluations

Part 5 A – Initial Imaging Findings at 5-7 year Follow Up

(comparison with previous time points of evaluation)

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5-Year imaging sequelae of concussive blast injury and relation to early clinical outcome

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Group Level Diffusion Tensor Imaging and Quantitative Volumetric Results

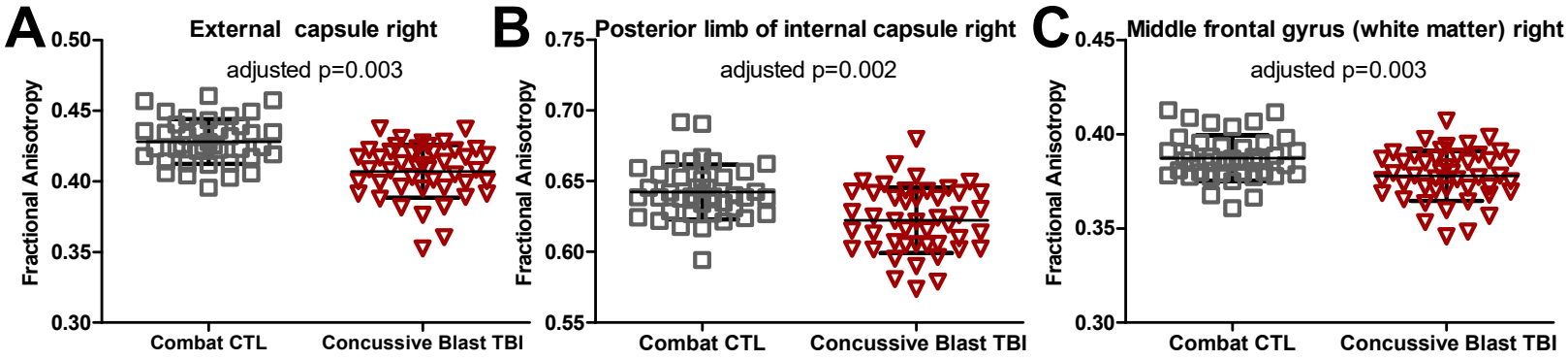

Table 2. Volumetric Analysis

Region (volume in mm^3)	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

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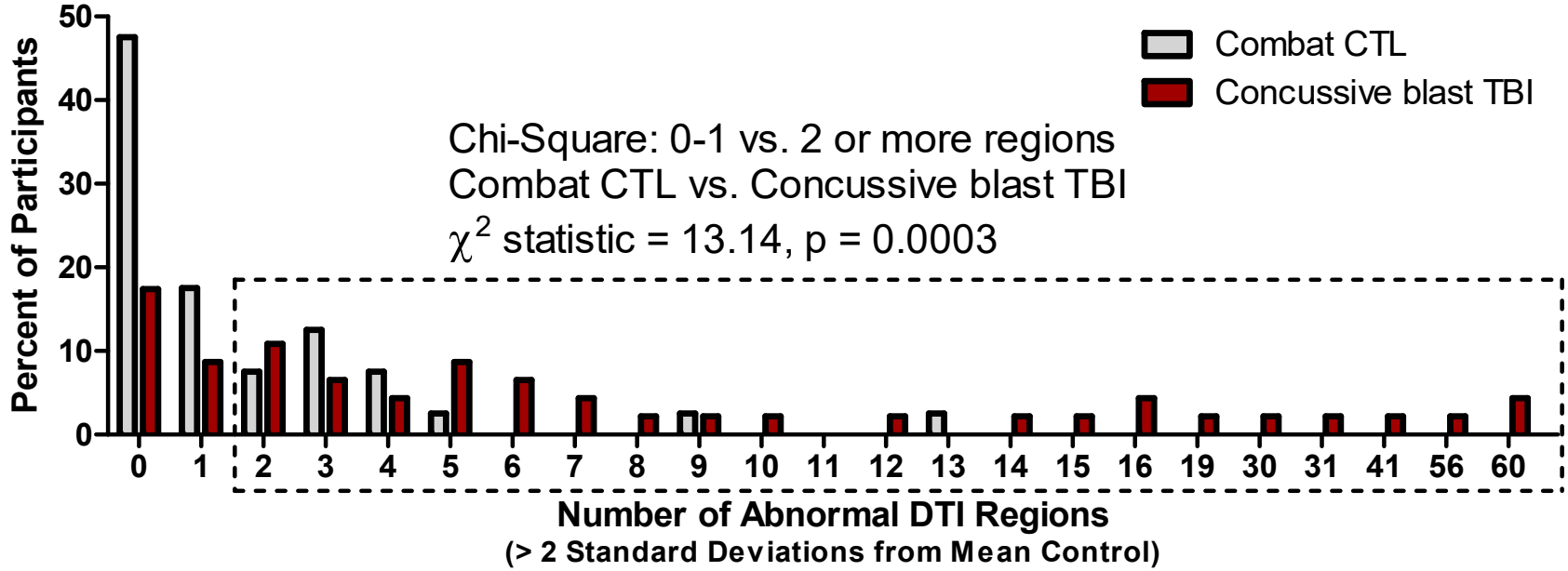
~5 year post-injury DTI abnormalities by Patient following blast concussion



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

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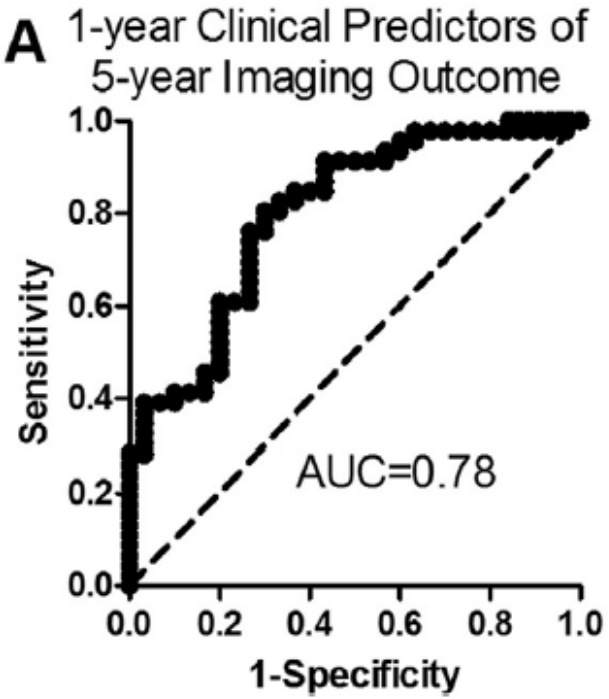
Predictors of Imaging Outcome at ~5 years post-injury

A



B

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	4.52	(1.32 : 15.47)	0.0	TBI Diagnosis
Age at Injury	1.09	(1.01 : 1.18)	0.03	Older Age
Verbal Memory	1.54	(0.85 : 2.79)	0.16	Less Verbal Recall
Verbal Fluency	0.93	(0.87 : 1.00)	0.05	Less Word Generation

Logistic regression leveraging clinical and demographic data collected in the acute/sub-acute and 1-year follow up in addition to exposures between 1-year and 5-year follow up to identify predictors of these long-term imaging changes determined that concussion diagnosis (acute), older age at injury (acute), verbal memory (1yr) and verbal fluency (1yr) best predicted the presence of DTI abnormalities 5 years post injury (AUC 0.78 indicating good prediction strength)

Mac Donald, et al, NeuroImage:Clinical 2017

Part 5 B – Initial Clinical Findings at 5-7 year Follow Up

(comparison with previous time points of evaluation)

Research

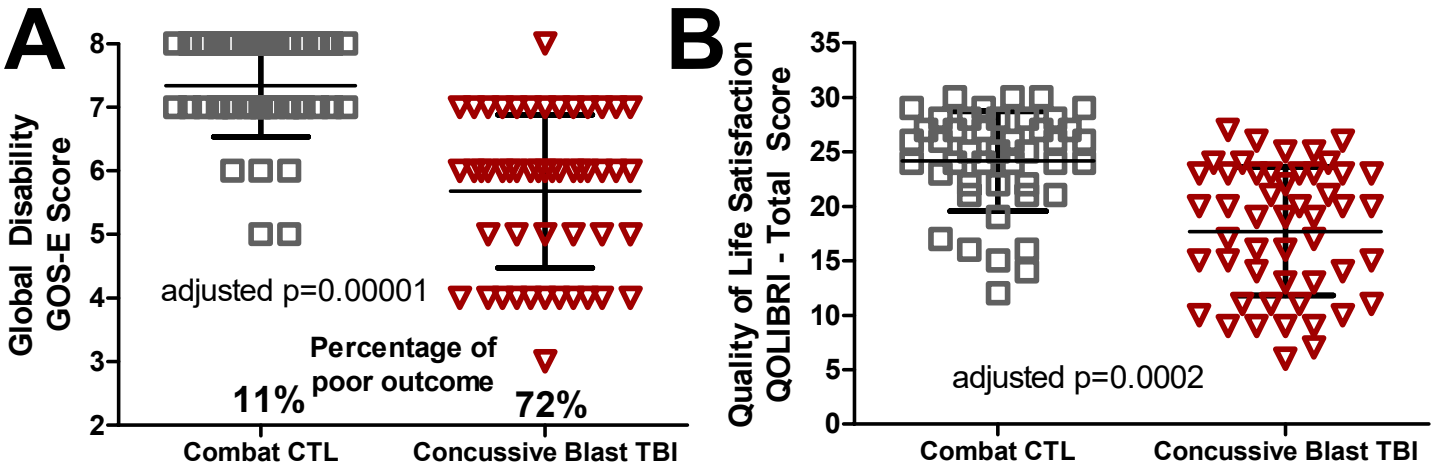
JAMA Neurology | Original Investigation

Early Clinical Predictors of 5-Year Outcome After Concussive Blast Traumatic Brain Injury

Christine L. Mac Donald, PhD; Jason Barber, MS; Mary Jordan, MA; Ann M. Johnson; Sureyya Dikmen, PhD; Jesse R. Fann, MD, PhD; Nancy Temkin, PhD

JAMA Neurol. doi:10.1001/jamaneurol.2017.0143
Published online May 1, 2017.

Global Disability at ~5 year follow up

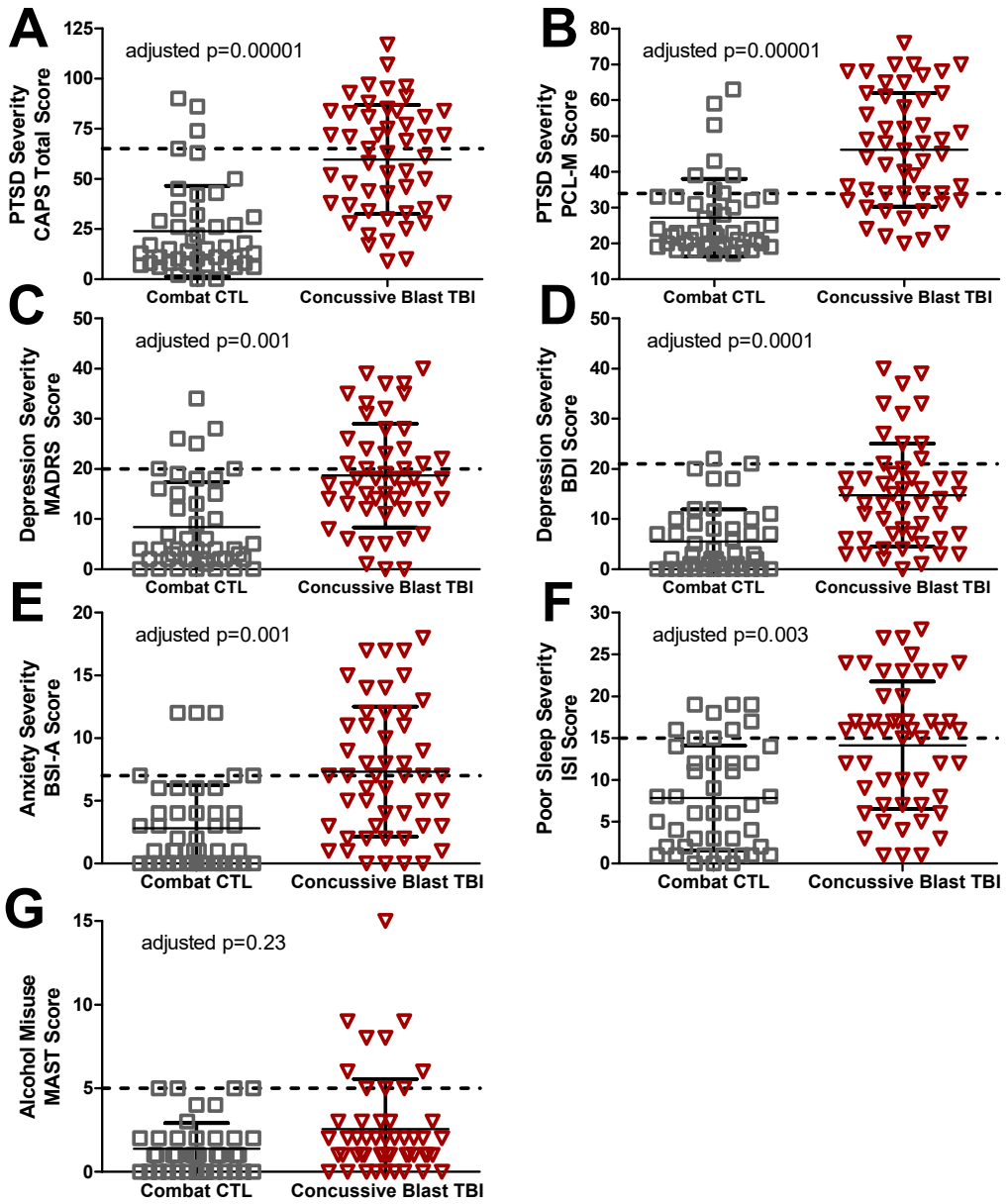


- Overall disability and quality of life were significantly impacted in the concussive blast group compared to combat-deployed controls

- 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

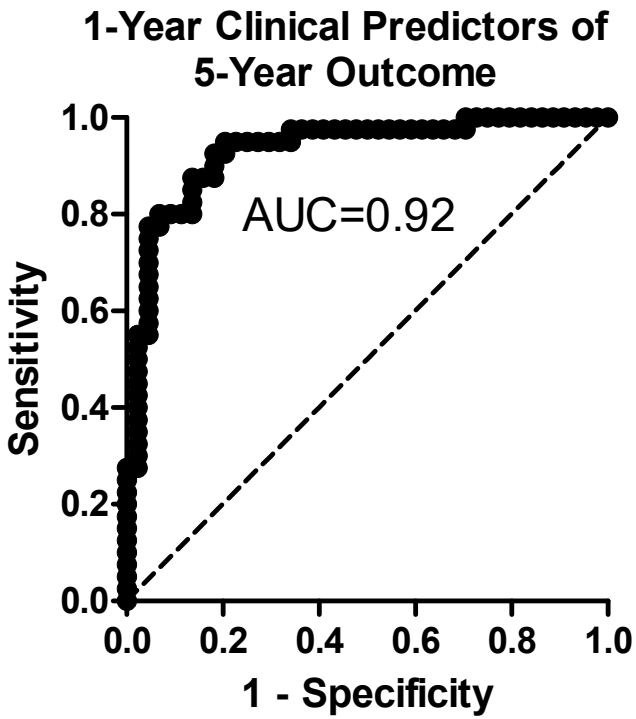
Mental Health at ~5 year follow up



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.
- Comparing 1- and 5-year PTSD data in the same participant, 21% of controls and 38% of concussive blast showed significant worsening of symptoms.
- Both groups had ~ 20% with substantial exacerbation in depression during this same time period
- Surprising to us, 41% combat controls and 80% of concussive blast patients endorsed seeking help for their mental health symptoms while only ~19% of each group found sustained resolution

Predictors of Poor Clinical Outcome at ~5 years post-injury



Best 1-Year Predictors of 5-Year Poor Outcome				
Parameter	**Odds Ratio**	**95% Confidence Interval**	**P-value**	**Predictor Direction**
Clinical Status: Control or TBI	4.65	(0.95 : 22.78)	0.058	TBI Diagnosis
Neurobehavioral Symptoms	1.30	(1.09 : 1.55)	0.004	Higher Symptoms
Motor Strength, Coordination	1.87	(0.83 : 4.21)	0.13	Slower Walk
Pre-Injury Intelligence	1.07	(1.01 : 1.14)	0.02	Lower Intelligence
Verbal Fluency	0.95	(0.88 : 1.02)	0.17	Less Word Generation

Logistic regression leveraging clinical and demographic data collected in the acute/sub-acute and 1-year follow up in addition to exposures between 1-year and 5-year follow up to identify predictors of poor clinical outcome determined that concussion diagnosis (acute), neurobehavioral symptoms (1yr), motor strength (1yr), pre-injury intelligence, and verbal fluency (1yr) best predicted 5 year poor GOS-E scores (AUC 0.92 indicating excellent prediction strength)

Mac Donald, et al, JAMA Neurology 2017

Part 5 Summary: Comparison of ~1 to ~5 year outcome

- 74% of the concussive blast TBI cohort had reductions in fractional anisotropy indicative of chronic brain injury while conventional imaging was normal at ~5 year follow up

- Predictors of poor imaging outcome by DTI abnormalities included concussion diagnosis, older age at injury, and 1 year verbal memory and verbal fluency

- Many concussive blast patients experience evolution NOT resolution of symptoms from 1 to 5 year follow up
  - 72% had worsening global disability (GOS-E)
  - 38% had worsening PSTD symptoms (CAPS)
  - 20% had worsening depression symptoms (MADRS)
- 80% in fact sought assistance for mental health challenges during this time frame and completed their treatment
- Yet - only 18% had sustained resolution!

- Predictors of poor clinical outcome included diagnosis of concussion, pre-injury intelligence, and 1 year neurobehavior symptoms, motor strength, verbal fluency
  - NOTE: Neurobehavior was assessed using the clinician structured interview – Neurobehavioral Rating Scale, Revised - a 29-domain measure of neurological, cognitive, and mental health function

Summary of Findings from the EVOLVE Study

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

- 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.
- Combat concussion appears to worsen global outcome at 1 year and 5 year follow up.
- Combat Concussion exacerbates symptoms of mental health severity which we observed repeatedly across 4 independent cohorts
- Important 'Points of Comparison'
  - NO difference between non-medically evacuated & medically evacuated concussion at 1 year follow up
  - NO difference between blast & non-blast concussion at 1 year follow up
  - YES difference between blast-exposed controls and non-blast exposed controls at 1 year follow up
- 80% of blast concussion patients sought assistance for mental health issues by 5 year follow up BUT only 18% had sustained resolution of their symptoms.
- Majority of combat concussion patients exhibit an evolution NOT resolution of symptoms from 1 to 5 year follow up.
- These findings suggest a greater impact of combat-related concussion on long term outcome than previously appreciated.

The Public Health Impact and Rising Cost

- Peak year for payout on disability compensation to US involvement in World War I (1917-1919) was 1969, World War II (1941–1945) was 1980.
- Vietnam (1955-1975) disability payout is still on the rise.
- With estimated compensation costs from the 'Global War on Terror' (2001-2014) nearing $1 trillion in the coming years, true cost impact is still yet to be appreciated
- Service members today have decades of life to live with the debilitating effects of brain injury and mental illness among other disabilities.
- Mortality rates have decreased while morbidity rates have substantially risen
- Our focus must now be on Long Term Quality of Life

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

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Follow up comments/questions can be directed to: cmacd@uw.edu