SUPPLEMENTAL MATERIAL:

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"**Prospectively Assessed Clinical Outcomes in Concussive Blast vs. Non-blast Traumatic Brain Injury in Evacuated US Military Personnel.**"

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1.SUPPLEMENTAL METHODS

1.1 Approval

The research protocol was approved by the Human Research Protection Office at Washington University, the Institutional Review Board for LRMC at Brooke Army Medical Center, and the Clinical Investigation Regulatory and Human Research Protection Offices of the U.S. Army Medical Research and Materiel Command.

1.2 Inclusion Criteria

Inclusion criteria for the TBI groups were as follows: 1) a positive screen for TBI at LRMC based on standard US military clinical criteria[1] including self-report of blast exposure or non-blast mechanism such as blunt trauma resulting in loss of consciousness, amnesia for the event, or change in neurological status, 2) injury from blast or non-blast mechanisms of injury within 30 days of enrollment, 3) US military, 4) ability to provide informed consent in person, 5) no contraindications to MRI such as retained metallic fragments, 6) no prior history of moderate to severe TBI based on Department of Defense criteria, 7) no prior history of major psychiatric disorder, 8) agreement to communicate by telephone or email monthly for 6-12 months and then travel to Washington University for in-person follow-up. Inclusion criteria for the control groups were the same except for a negative screen for TBI at LRMC with or without a history of blast exposure.

1.3 Informed Consent

Competence to provide informed consent was assessed in a standardized fashion based on responses to questions regarding the purpose of the study, expected requirements for participation, and potential risks. Additional written consent was obtained from the subjects at the time of follow-up at Washington University. Active duty military subjects were not paid for participation, though travel expenses to St Louis were covered. Subjects not on active military duty status at the time of follow-up in St Louis were paid $240 plus travel expenses for participation.

1.4 Clinical Histories

Medical documentation regarding duration of loss of consciousness and post-traumatic amnesia was often not available or not reliable. All available clinical histories indicated change in level of consciousness or loss of consciousness for a few minutes and post-traumatic amnesia for less than 24 hours. The requirement for in-person informed consent made more severe TBI patients typically not eligible and none were enrolled. No intracranial abnormalities were detected on non-contrast head CT. Thus, all TBI subjects met the DoD criteria for uncomplicated 'mild' TBI. While previous literature has used the term 'mild' to describe TBI on the lower end of the spectrum of severity, we now prefer the term 'concussive' to describe these injuries.

In addition, initial records of clinical status in TBI subjects assessed at LRMC using the military acute concussion evaluation (MACE) [1] were reviewed. This brief cognitive test assesses orientation, immediate verbal memory, concentration, and short term delayed verbal memory.

1.5 Reasons for Lack of Follow Up

Reasons for inability of subjects to follow-up at Washington University included redeployment to Afghanistan, reassignment to military position overseas, inability or unwillingness to travel to St. Louis, withdrawal of consent, and inability to maintain telephone or email contact. 5 subjects were disqualified at the time of follow up due to readily apparent malingering (n=3) and/or unwillingness to complete the necessary assessments (n=2).

1.6 Glasgow Outcome Scale Extended

The last assessment prior to in-person follow-up was considered the final outcome. Information was gathered separately from both the subject and a collateral source (typically a spouse, parent, or sibling) whenever possible. When

information collected from the subject and the collateral source differed, the worse outcome was used. The GOS-E is scored from 1-8: 1=dead, 2=vegetative, 3-4=severe disability, 5-6=moderate disability, 7-8=good recovery. Moderate disability (GOS-E = 5-6) is defined as one or more of the following: 1) inability to work to previous capacity 2) inability to resume the majority of regular social and leisure activities outside the home 3) psychological problems which have frequently resulted in ongoing family disruption or disruption of friendships. Severe disability is defined as reduced ability to perform activities of daily living such that supervision is required. Standardized, structured interviews were performed according to published guidelines [2].

1.7 Data Safety and Monitoring

Subjects were assigned a random 4 digit code number to protect confidentiality and all research data was identified by code number only. A board certified psychiatrist (Dr. Nelson) was immediately available in case the CAPS examination exacerbated PTSD symptoms. No exacerbations requiring medical intervention occurred, though additional support from study staff was required on several occasions.

For clinical evaluations, the principal investigator audited 1 in 10 randomly selected subjects' data sets to ensure that data was scored and entered correctly. These audits revealed only minor discrepancies in scoring criteria which were then corrected across the entire cohort of subjects.

1.8 Subject Examination Details

Subjects took all medications as prescribed by their clinical providers. All tests were performed between 9 am and 5 pm in private, quiet, well-lighted rooms. All examiners were clinicians who underwent standardized training in administering the assessments. The standardized neurological exam and interview required approximately 1 hour per subject. The psychiatric assessments and neuropsychological test battery both required approximately 2 hours per subject.

The neuropsychological test battery consisted of the following: Conner's Continuous Performance Test II [3], a computer-based assessment of attention, impulsivity, reaction time, and vigilance; the California Verbal Learning Test II [4], an assessment of verbal declarative memory; the 25 hole grooved pegboard test [5], an assessment of upper extremity motor speed and coordination; a timed 25 foot walk; the Trail Making test [6], an assessment of visual scanning, coordination and mental flexibility; the Controlled Oral Word Association test [7], an assessment of verbal fluency; the Wechsler Test of Adult Reading [8] as an estimate of pre-injury verbal intelligence; the Iowa Gambling Test[9], a computer-based assessment of impulsivity and decision making; the D-KEFS Color-Word Interference Test [10], an multi-domain assessment of executive function similar to the Stroop test; and the Ruff-Light Trail Learning Test[11], an assessment of visual-spatial memory. A relatively easy forced choice test embedded in the California Verbal Learning Test was used to assess adequacy of effort.

1.9 Statistical Analysis

All data was analyzed using Statistica10.0 (Statsoft Inc). Continuous variables have been summarized as mean ± standard deviation unless otherwise specified. The normal distribution of each continuous variable was assessed using the Shapiro-Wilk test. For normally distributed variables, Analysis of Variance and student's t tests were used to compare groups. For non-normally distributed variables, the nonparametric Kruskal-Wallis Tests and Mann-Whitney U (MWU) tests were used. We pre-specified the hypothesis that TBI subjects would have worse outcomes than controls, but did not pre-specify any hypotheses regarding blast + impact TBI vs non-blast TBI subjects. One-sided tests were used when hypotheses were pre-specified, and two-sided tests were used otherwise.

In addition to between group comparisons, individual subject data from neuropsychological testing was analyzed. Specifically, an individual subject's performance was considered abnormal if it was worse than two standard deviations below the mean of the performance of the non-blast control group. The number of tests for which performance was abnormal for each subject was then tabulated. To determine the number of abnormal tests that would expected by chance, the binomial distribution was used with p=0.02275 and n=18 for the 18 neuropsychological variables examined (eTable 2). Prior to this analysis, all neuropsychological variables were confirmed to be statistically independent as is required by the assumptions of this approach.

For correlation analyses, nonparametric rank-based Spearman correlations were utilized. Pearson correlations were attempted, but the residuals were not normally distributed as determined by the Shapiro Wilk test.

Logistic regression analysis was utilized to explore the relationship between global outcome and multiple quantitative measures of specific symptoms and impairments. The Statistica 10.0 'generalized linear/nonlinear model building' algorithm was used with the selection of the 'logit' link function. This algorithm generated a distinct model for each possible subset of quantitative measures of specific symptoms and impairments. Models were then ranked by Akaike information criterion. Detailed data and receiver-operator curves (ROC) were then generated for the top ranked models. Step-wise forward entry and step-wise removal of variables was also performed, which yielded identical results.

2. SUPPLEMENTAL RESULTS

2.1 Glasgow Outcome Scale Extended

At an individual subject level, 41/53 blast + impact TBI subjects (77%) and 23/29 non-blast TBI subjects (79%) had moderate to severe disability defined as GOS-E score of 6 or less. 16/27 blast controls (59%) and 28/69 non-blast controls (41%) also met this criteria. The disabled proportion was significantly greater in non-blast TBI subjects in comparison to non-blast controls (p=0.0005, chi-square). Blast controls and non-blast controls did not significantly differ (p=0.10, chi-square), nor did blast controls and blast + impact TBI subjects (p=0.09, chi-square) or blast + impact TBI and non-blast TBI subjects (p=0.84, chi-square) in proportion of disabled subjects.

The above results were derived only from subjects who were available for in-person follow-up. However, the outcomes in the subjects not available for in person follow-up 6-12 months after enrollment did not differ from those that were available for follow-up based on GOS-E obtained by telephone and email (p-value range across groups 0.46-0.85, MWU tests).

2.2 Military Acute Concussion Evaluation

Scores on the military acute concussion evaluation (MACE) completed after medical evacuation to Landstuhl, Germany did not significantly differ between non-blast and blast + impact TBI subjects (25.32 ± 3.36 non-blast TBI, 24.8 ± 3.22 blast + impact TBI, p=0.42, 2-sided Student's t) suggesting similar levels of initial concussion impairment. MACE was not performed in the control subjects.

2.3 Neuropsychological Test Abnormalities

There were few statistically significant differences between groups. Significantly worse performance was noted in the non-blast TBI group in comparison to the non-blast controls on 25-foot walk (p=0.0024), and Grooved Peg Board (p=0.0027). There were no differences in performance in the blast control vs. non-blast control groups, blast + impact TBI vs. blast control groups, or blast + impact TBI vs. non-blast TBI groups.

2.4 Neurobehavioral Assessment

Clinician ratings in multiple neurobehavioral domains using the neurobehavioral rating scale-revised revealed more substantial impairments in the TBI subjects compared with controls (eFigure1). However, there were no significant differences between blast + impact TBI and non-blast TBI patients (NRS total:p=0.93, mood/affect:p=0.18, executive/cognitive:p=0.92, oral/motor:p=0.29, positive symptoms:p=0.39, negative symptoms:p=0.62, MWU). Comparisons between non-blast TBI and non-blast controls indicated more substantial impairments overall and in several specific domains. (Total NRS:p=0.000001, mood/affect:p=0.000007, executive/cognitive:p=0.00002, oral/motor:p=0.0001, positive symptoms:p=0.08, negative symptoms:p=0.002, MWU).

Somewhat surprisingly, the blast + impact TBI group did not differ significantly from the blast control group, though there were trends towards greater impairments in the blast + impact TBI group. (Total NRS:p=0.08, mood/affect:p=0.18, executive/cognitive:p=0.17, oral/motor p=0.57, positive symptoms p=0.31, negative symptoms:p=0.14, MWU).

There were also more severe neurobehavioral impairments in blast controls compared with non-blast controls. There were significant differences on total NRS (p=0.0004), and mood/affect (p=0.0008), executive/cognitive (p=0.007), negative symptoms (p=0.01) subdomains (MWU). Oral/motor (p=0.06) and positive symptom (p=0.16) subdomains were not significantly different.

2.5 Headache Impairment

Similar to the results for MIDAS, there were also no significant differences on the HIT-6 between non-blast TBI and blast + impact TBI patients (eFigure 4) (HIT-6:p=0.22, Severe headache pain:p=0.56, Headache limited abilities:p=0.96, Subject wishes to lie down:p=0.04, Tired due to headache:p=0.05, Irritated due to headache:p=0.08; Headache limited concentration:p=0.88, MWU). Non-blast TBI subjects showed significantly higher levels of headache impairment in comparison to non-blast controls on the HIT-6 (p=0.0000001) and on all of the specific questions (Severe headache pain:p=0.002, Headache limited abilities:p=0.0004, Subject wishes to lie down:p=0.000001, Tired due to headache:p=0.0000001, Irritated due to headache:p=0.0000001, Headache limited concentration:p=0.0000001; MWU). Blast controls had more impairment than non-blast controls on the HIT-6 total (p=0.0009), severe headache pain, (p=0.008) and headache limited abilities (p=0.009). There was no significant differences on the HIT-6 between blast + impact TBI and blast controls (HIT-6:p=0.09; Severe headache pain:p=0.67, Headache limited abilities:p=0.26, Subject wishes to lie down:p=0.21, Tired due to headache:p=0.06, Irritated due to headache:p=0.06, Headache limited concentration:p=0.011, MWU). While 23% of non-blast controls were found to have impairment due to headache significant enough warrant suggested follow up with a physician by the HIT-6 criteria[12], 46% of blast control, 64% of blast + impact TBI, and 83% of non-blast TBI subjects also met this criterion.

2.6 Logistic Regression Modeling for Dichotomized Glasgow Outcome Scale Extended

The second best model included number of neuropsychological abnormalities, depression severity, overall headache-related impairment, and severity of neurological deficits. The third best model was similar to the first model but substituted overall headache-related impairment for headache-related disability. Identical results were obtained using step-wise forward entry and step-wise removal of variables (not shown).

3. SUPPLEMENTAL DISCUSSION

The general lack of neuropsychological findings by group is in line with previous work[13,14]. However our single subject level analysis uncovered significantly impaired performance in subsets of subjects from both TBI groups. Thus, an implication of this study is that single subject level analyses should be considered for this type of research.

The overall findings regarding headache impact were also consistent with prior reports although on the higher side of the very broad range of previously published prevalence following concussive brain injury[15]. While 23% of non-blast controls were found to have impairment due to headache significant enough warrant suggested follow up with a physician by the HIT-6[12] criteria, 46% of blast control, 64% of blast + impact TBI, and 83% of non-blast TBI also met this criterion. This is higher than the 20% previously reported in the military following concussion[16], but within the broad range of 18-90% noted in prior studies of individuals with post-traumatic headache following 'mild' brain injury [15,17-22].

A surprising finding from this study was that combat exposure intensity did not correlate with PTSD severity in the TBI subjects, but did correlate with PTSD severity in the controls. Many explanations for this relationship are possible. First, the relationship could have occurred by chance, as the p-value for the interaction between group and combat exposure intensity was marginal. Second, the self-reported measure of combat exposure intensity, the CES, may not accurately capture the war-time experiences that drive PTSD severity. Third, and most intriguingly, is the hypothesis that there may be phenocopies of PTSD-like symptoms that cannot be distinguished using the CAPS; TBI-related emotional dysregulation due to structural injury to brain circuits could be indistinguishable using clinical evaluations alone from the psychological effects of combat and other stressful life experiences.

This study and prior work have identified very high levels of co-occurring post-traumatic headache and PTSD following 'mild' TBI in veterans[23-25]. Future work will be required to understand the underlying mechanism of how concussive brain injury contributes to poor psychiatric outcome and significant headache impairment in this population. For example, it has been suggested by others that signaling involving the pituitary adeylate cyclase-activating peptide (PACAP) may be involved in the pathogenesis of both PTSD and migraine headache[26,27]. PACAP is known to regulate

cellular stress response and was recently found to have a strong association with PTSD diagnosis in both clinical studies of traumatized individuals and preclinical models fear physiology[26]. It has also been implicated in a recent study as a potent vasodilator in dural vasculature; specifically the middle meningeal artery, suggesting it may play an important role in the development of migraine[27]. It is possible that a better understanding of this relationship will lead to new treatments for both phenomena positively impacting outcome in these patients. Likewise, other potential contributions to headache such as cervical segmental joint dysfunction, neck flexor endurance, or neck musculature tightness, among others that are commonly known to contribute to chronic post-traumatic headache[28].

The finding of significant olfactory deficits in the non-blast TBI group warrants further investigation and possibly lends support to the hypothesis that structural brain injury contributed to outcomes; The location of the olfactory bulbs are adjacent to brain anatomy thought to be involved in emotion regulation. Injury to the region in general may be contributing to both deficits in olfaction as well as the inability to extinguish fear memories and thus the exacerbation of PTSD symptomatology. In future studies, more thorough examination of the olfactory bulbs would be required including focused high resolution imaging of the structure itself and comprehensive, repeated quantitative assessment of olfactory acuity.

4. SUPPLEMENTAL TABLES AND FIGURES

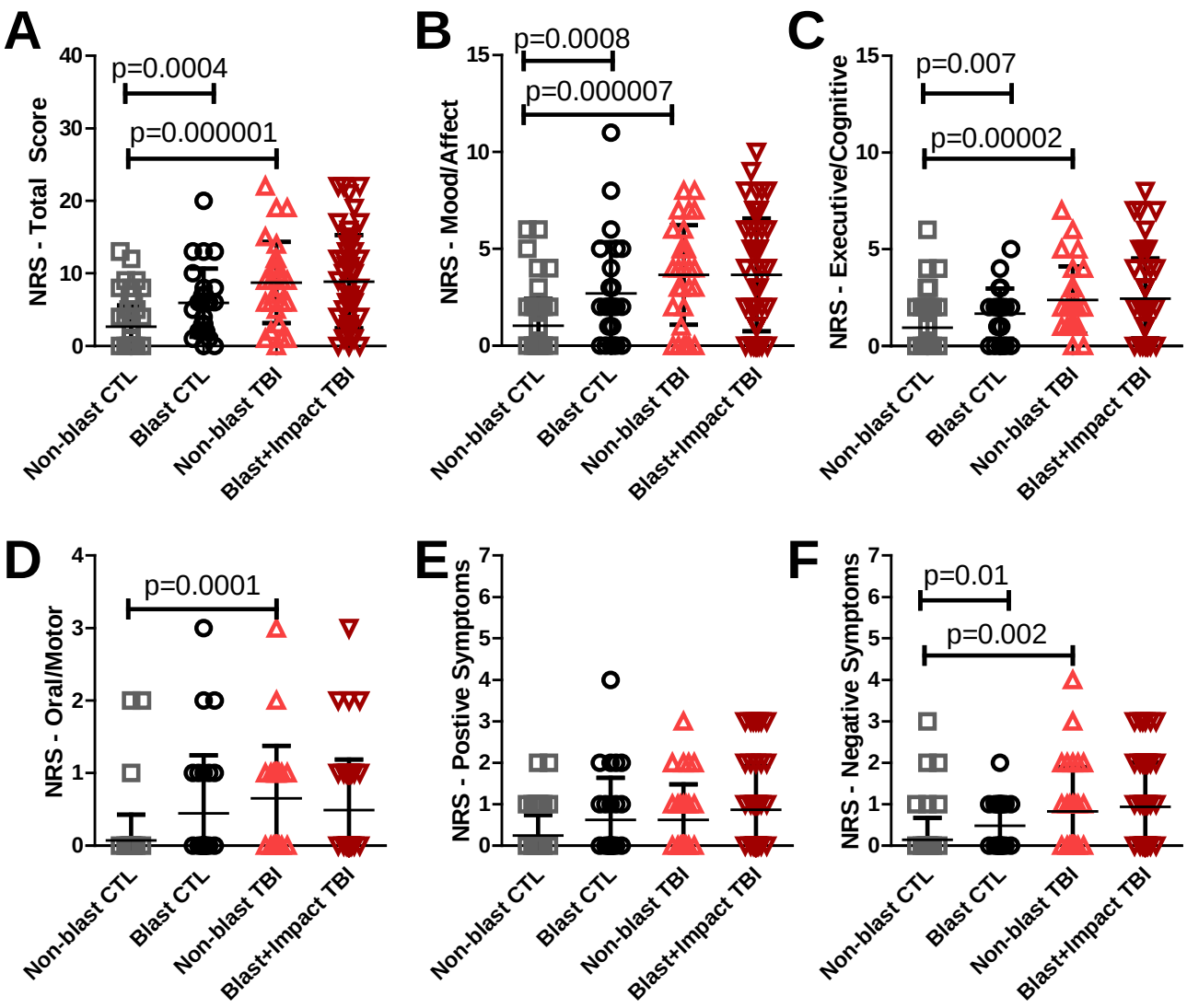
Group	Total Enrolled	Completed Follow UP	Disqualified at Follow up	Final Group Size
Non-blast CTL	97	71	2	69
Blast CTL	35	27	0	27
Non-blast TBI	44	32	3	29
Blast + impact TBI	79	53	0	53
TOTAL	255	183	5	178

eTable 1. Group enrollment and 6-12 month follow up attrition.

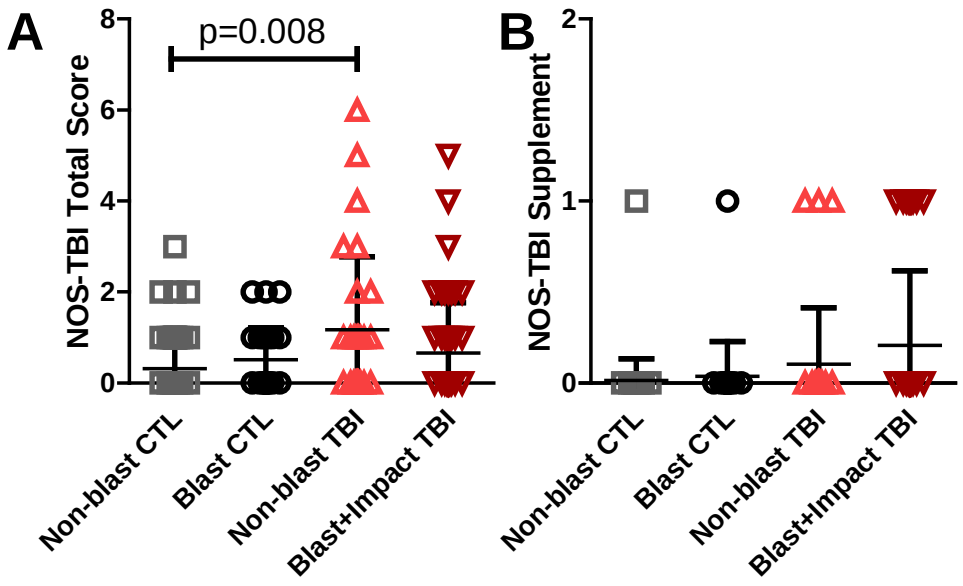
eTable 2. Neuropsychological Test Performance

Test	Non Blast CTL (n=69)	Blast CTL (n=27)	Non Blast TBI (n=29)	Blast + impact TBI (n=53)
25-Foot Walk (seconds)				
(Motor Strength, Balance, Coordination)	3.92 ± 0.82	4.22 ± 0.66	4.76 ± 1.16 [A]	4.59 ± 1.17
Conners' Continuous Performance Test II				
Omission Errors (T-score):				
(*Attention Lapses*)	48.29 ± 12.17	47.45 ± 7.51	53.30 ± 15.11	56.06 ± 19.8
Commission Errors (T-score):				
(*Impulsivity*)	50.40 ± 10.60	50.02 ± 8.19	52.46 ± 9.81	54.05 ± 10.6
Hit Rate (T-score):				
(*Reaction Time*)	48.94 ± 11.72	48.98 ± 8.67	52.10 ± 12.22	47.83 ± 8.63
Hit Rate Block Change (T-score):				
(*Sustained Vigilance)*	52.05 ± 10.62	48.01 ± 8.82	51.64 ± 13.75	48.73 ± 12.0
Iowa Gambling Test (T-score)				
(Impulsivity)	49.52 ± 10.40	48.3 ± 9.65	47.62 ± 9.91	48.96 ± 11.1
Ruff-Light Trail Learning Test (T-score)				
Trials Correct *(Visual Memory)*	49.53 ± 11.10	52.52 ± 6.54	50.41 ± 10.10	49.24 ± 10.85
Wechsler Test of Adult Reading (Standard Score)				
(Estimate of Pre-injury Verbal Intelligence)	102.88 ± 14.55	100.56 ± 10.99	98.52 ± 11.10	99.49 ± 11.66
California Verbal Learning Test II				
Long-Delay Free Recall (Standard Score)				
(Verbal Memory)	-0.17 ± 1.10	-0.15 ± 0.95	-0.32 ± 1.27	-0.58 ± 1.21
Total Intrusions (Standard Score)				
(Falsely Recalled Items)	0.22 ± 1.00	0.22 ± 0.95	0.52 ± 1.42	0.45 ± 1.38
List B vs. Trial 1 List A (Standard Score)				
(Proactive Memory Interference)	0.08 ± 0.87	-0.15 ± 0.89	0.58 ± 1.03	-0.16 ± 1.12
Grooved Pegboard				
(Motor Speed & Coordination)				
Average Dom & Non-Dom Time (seconds)	69.03 ± 17.7	69.04 ± 10.56	75.84 ± 15.85 [B]	75.54 ± 15.52
Trail Making Test				
Trails A time (seconds)				
(Visual Scanning, Coordination)	22.10 ± 8.61	24.26 ± 7.41	26.57 ± 14.10	28.5 ± 16.69
Trails B time (seconds)				
(Trails A + Mental Flexibility)	57.12 ± 24.77	57.00 ± 14.97	67.52 ± 31.28	61.19 ± 21.40
Controlled Oral Word Association				
Total Score: *(Verbal Fluency)*	42.1 ± 10.18	40.37 ± 9.05	37.62 ± 9.98	37.75 ± 9.30
D-KEFS Color-Word Interference Test				
(Executive Function)				
Color & Word Naming (summed scaled score)	21.07 ± 4.98	18.67 ± 5.85	18.59 ± 7.25	18.64 ± 6.95
Inhibition (scaled score)	10.55 ± 3.02	10.19 ± 2.92	9.28 ± 4.57	9.83 ± 3.39
Inhibition/Switching (scaled score)	10.41 ± 2.88	9.30 ± 3.17	9.25 ± 4.16	9.29 ± 3.20

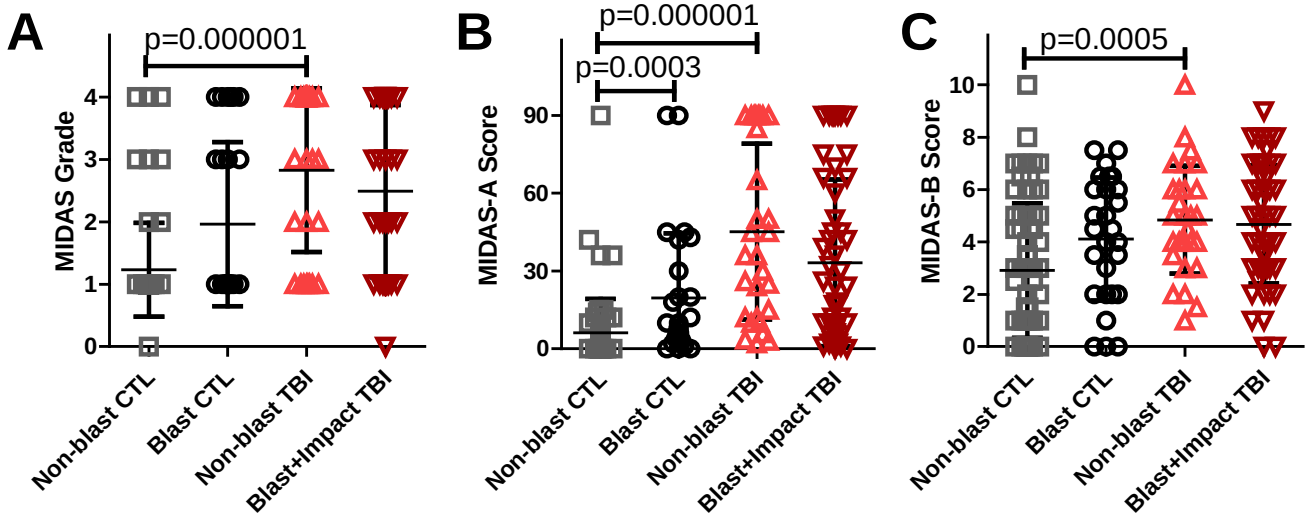
Superscripted letters indicate significance after correction for multiple comparisons ($p<0.0125$).
Uncorrected p-values are reported.
[A] Non-blast control vs. Non-blast TBI – Mann-Whitney U, p=0.0025
[B] Non-blast control vs. Non-blast TBI – Mann-Whitney U, p=0.0027



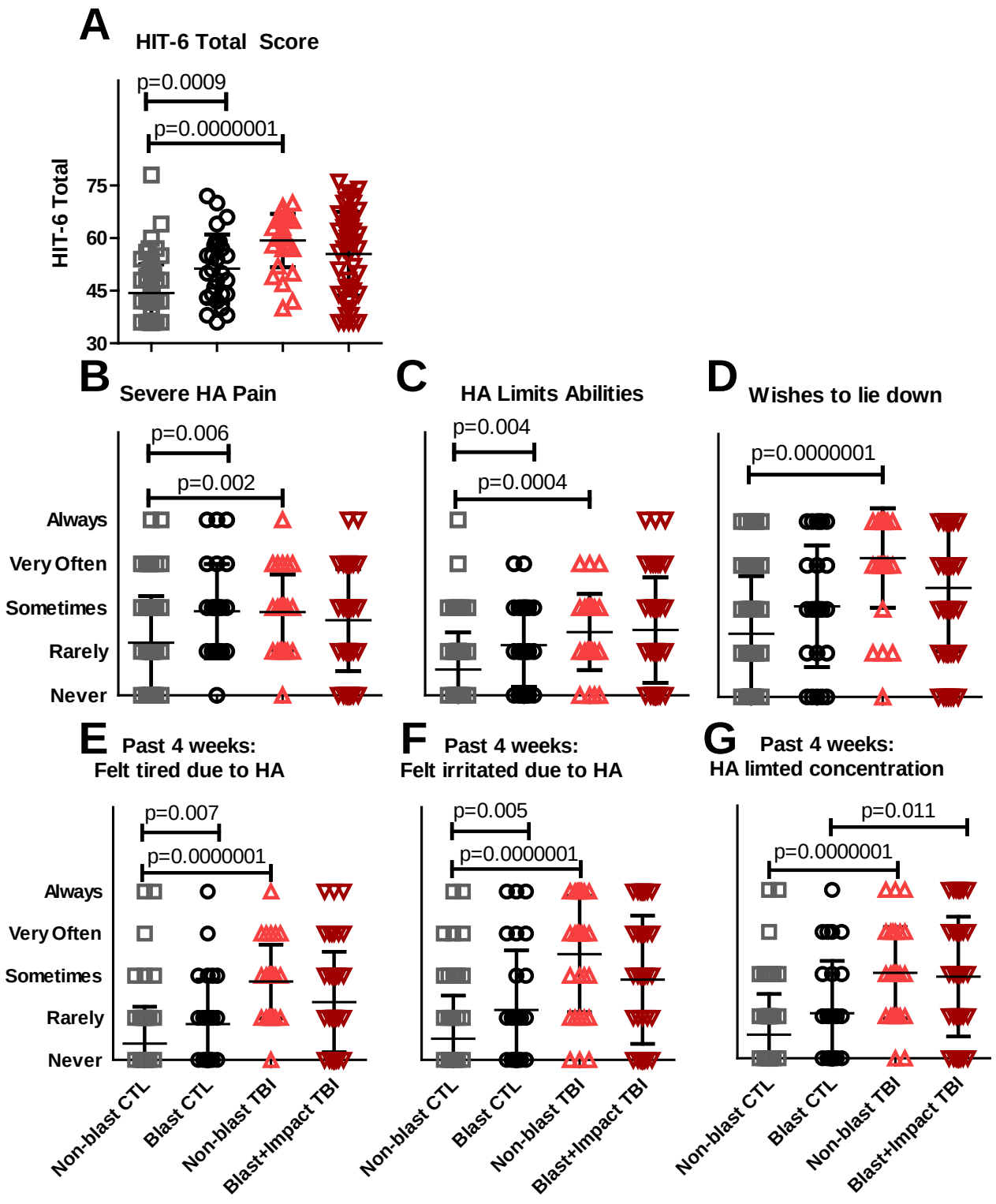
eFigure 1: Neurobehavioral measures of outcome. **A.** Neurobehavioral outcome assessed using the Neurological Rating Scale-Revised (NRS) Total Score: (Max 87). **B.** Mood/affect domain (Max 15). **C.** Executive/Cognitive domain (Max 24). **D.** Oral/motor domain (Max 12). **E.** Positive Symptoms domain (Max 21). **F.** Negative Symptoms domain (Max 12). Higher scores on all of the measures indicate worse impairment. P-values calculated using 1-tailed Mann-Whitney U tests and reported if significant after correction for multiple comparisons ($p<0.0125$).



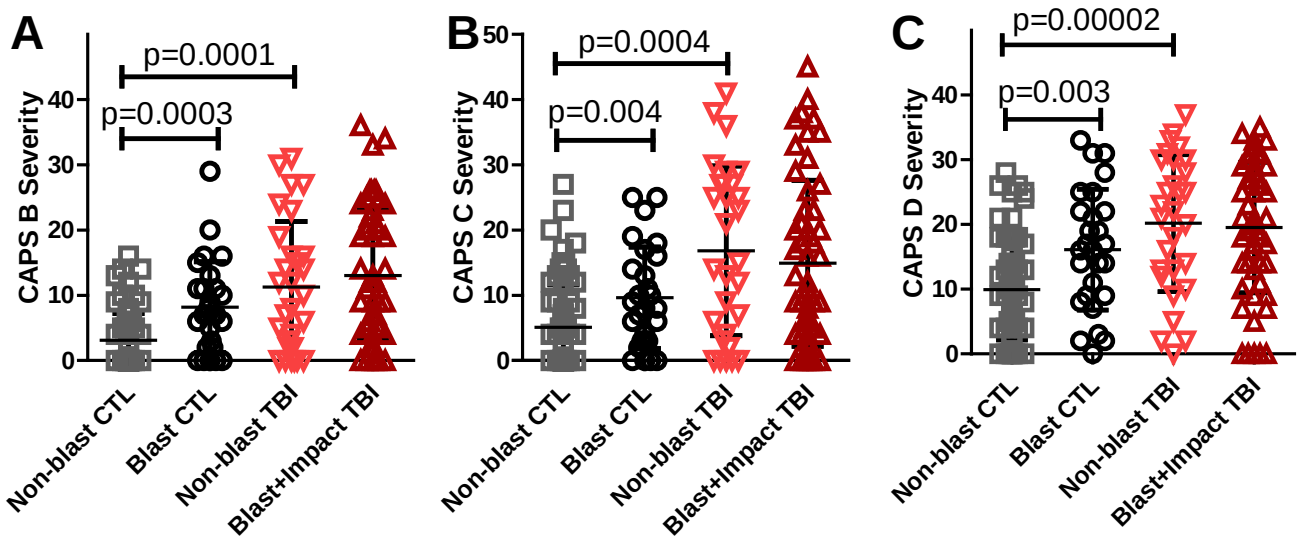
eFigure 2: Focal Neurological Deficits **A.** Focal neurological deficits commonly observed following traumatic brain injury assessed using the Neurological outcome scale for Traumatic Brain Injury (NOS-TBI). **B.** NOS-TBI Supplement for gait and limb ataxia. Higher scores on both measures indicate worse impairment. P-values calculated using 1-tailed Mann-Whitney U tests and reported if significant after correction for multiple comparisons ($p<0.0125$).



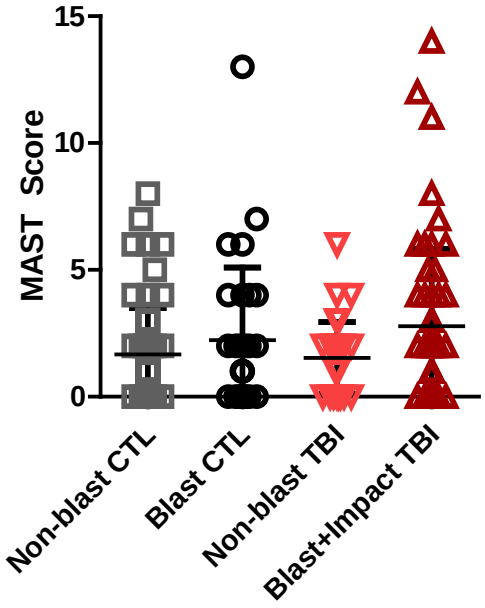
eFigure 3: Migraine Disability Assessment Subdomains. **A.** Total headache grade score for headache impact severity (Max 4). **B.** MIDAS-A assessment for headache frequency (Max 90). **C.** MIDAS-B assessment for headache pain (Max 10). Higher scores on all of the measures indicate worse impairment. P-values calculated using 1-tailed Mann-Whitney U tests and reported if significant after correction for multiple comparisons ($p<0.0125$).



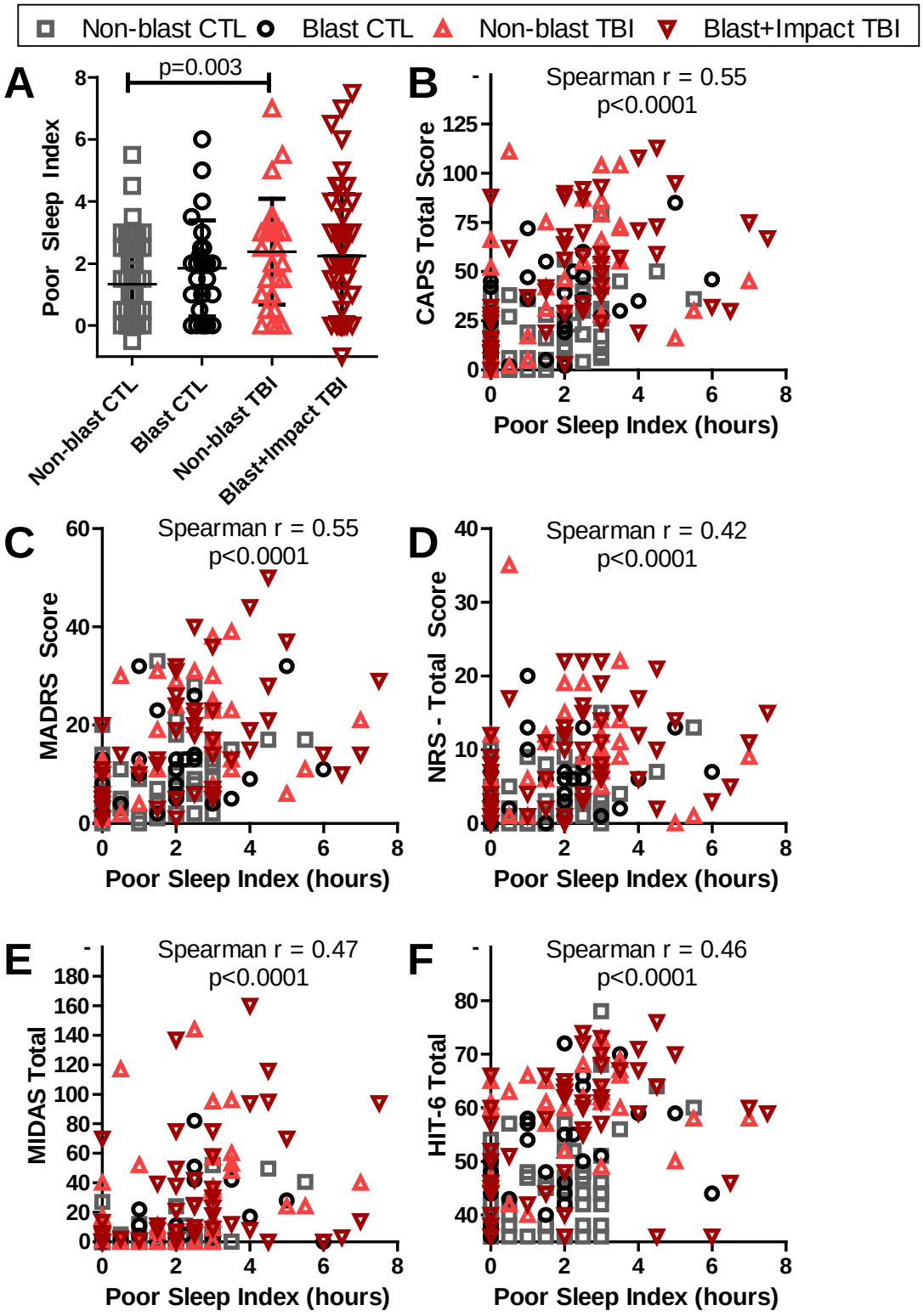
eFigure 4: Headache Impairment. **A.** Headache impairment assessed by the headache impact test (HIT-6) (Max 78). **B.** Frequency of severe headache pain. **C.** Frequency of headaches limiting ability to complete daily activities. **D.** Impact of headache determined by how often a subject wishes to lie down. **E.** Impact of headache in the past 4 weeks on how often a subject felt tired **F.** Impact of headache in the past 4 weeks on how often a subject felt fed up or irritated. **G.** Impact of headache in the past 4 weeks on how often a subject was limited in their concentration at work. P-values calculated using 1-tailed Mann-Whitney U and reported if significant after correction for multiple comparisons ($p<0.0125$).



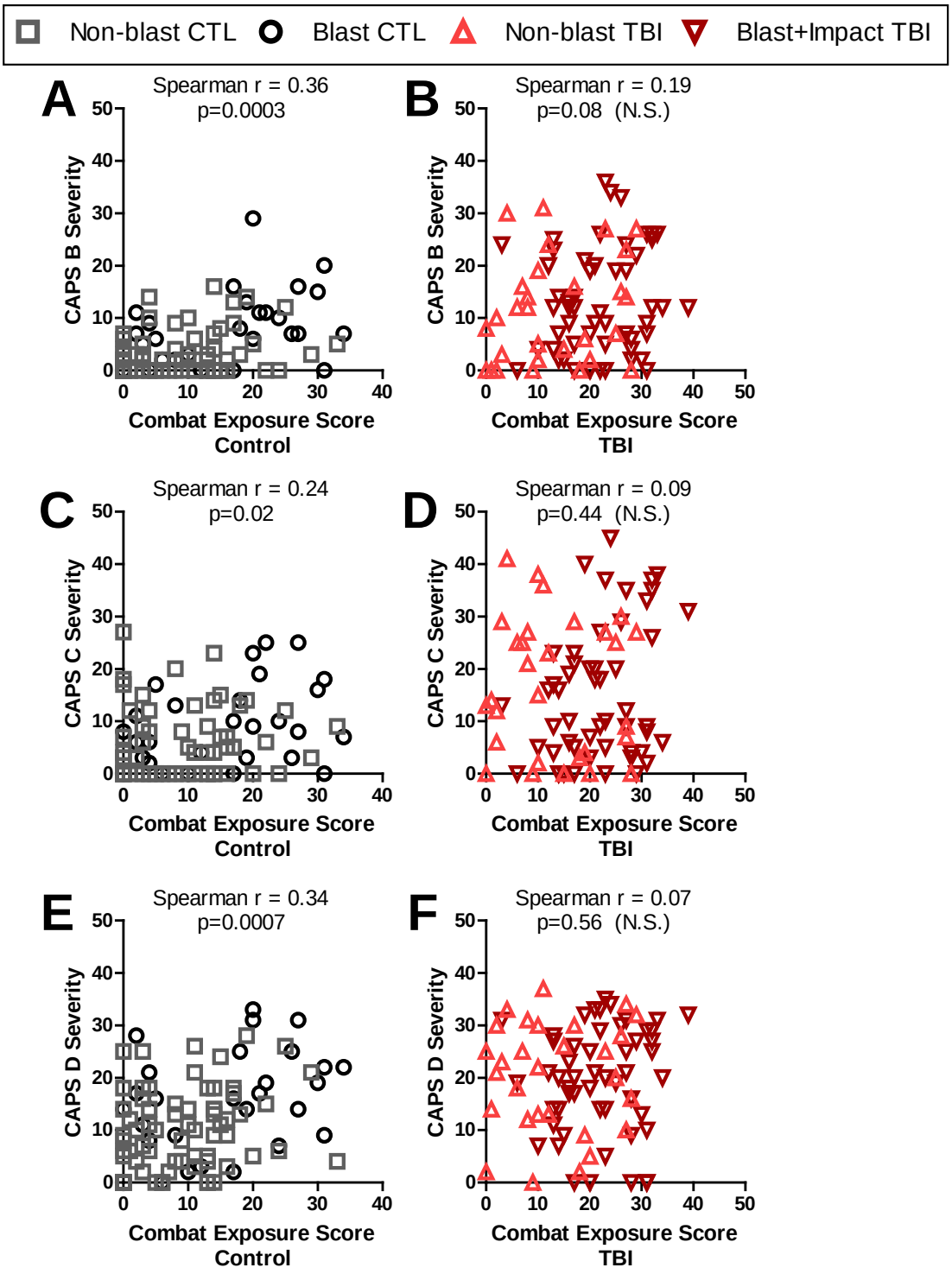
eFigure 5: Post-Traumatic Stress Disorder Severity Subdomains of the Clinician Administered PTSD scale for DSM IV (CAPS). **A.** CAPS B Severity – Re-experiencing (Max 40). **B.** CAPS C Severity – Avoidance and Numbing (Max 56). **C.** CAPS D Severity – Increased Arousal and hypervigilance (Max 40). Higher scores on all of the measures indicate worse impairment. P-values calculated using 1-tailed Mann-Whitney U tests and reported if significant after correction for multiple comparisons ($p<0.0125$).



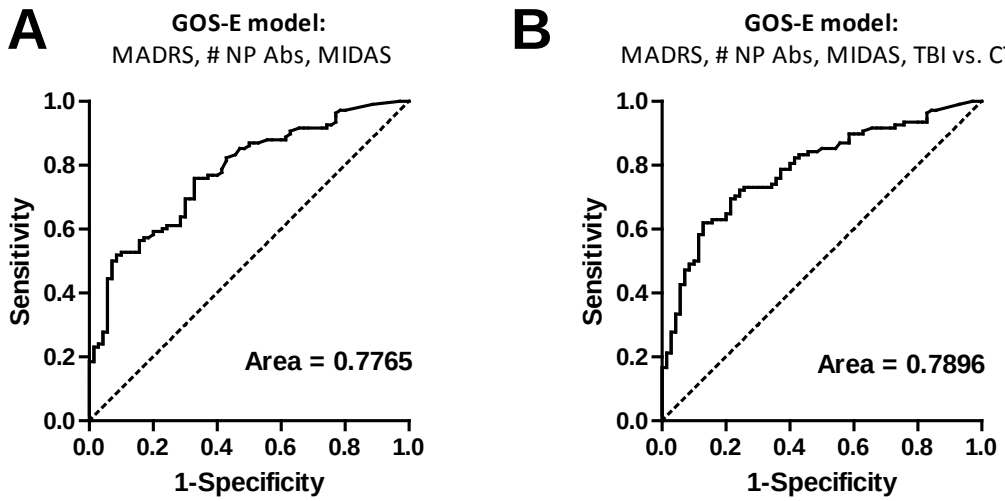
eFigure 6: Alcohol Misuse. Alcohol misuse was assessed using the Michigan Alcohol Screening Test (MAST: Max 22). No significant differences were observed across groups.



eFigure 7: Correlations between self-reported poor sleep index and measures of clinical evaluation. **A.** Poor sleep index, defined as the self-reported number of desired hours of sleep minus the number of acquired. **B.** Positive correlation with CAPS total severity for PTSD. **C.** Positive correlation with MADRS total severity for depression. **D.** Positive correlation with Neurobehavioral Rating Scale (NRS) for overall neurobehavioral outcome. **E.** Positive correlation with MIDAS for migraine disability. **F.** Positive correlation with HIT-6 for headache impact. Higher scores indicate worse impairment on all of the measures.



eFigure 8: Correlations between Clinician Administered PTSD Scale (CAPS) Subdomains and Intensity of Combat Exposure Scale (CES). **A**. Positive correlation between CAPS B severity (re-experiencing the traumatic event) and CES in control subjects. **B**. No correlation was observed between CAPS B severity and CES in the TBI groups. **C**. Positive correlation between CAPS C severity (avoidance and numbing) and CES in control subjects. **D**. No correlation was observed between CAPS C severity and CES in the TBI groups. **E**. Positive correlation between CAPS D severity (increased arousal and hypervigilance) and CES in control subjects. **F**. No correlation was observed between CAPS D severity and CES in the TBI groups.



eFigure 9: Receiver- Operator Curves for Logistic Regression Models of Global Outcome. **A**. Receiver-operator curve for best fit model of overall disability defined as the dichotomized GOS-E of 7 or 8 – good outcome, and = 6 or below –disabled. The best model included the total severity of depression based on the Montgomery Asberg Rating Scale (MADRS), the number of neuropsychological test abnormalities (# NP Abs), and the Migraine Disability Scale for headache impairment (MIDAS). **B**. Receiver-operator curve for logistic regression model of overall disability with addition of TBI vs Control as a categorical variable showing negligible improvement over the original best fit model.

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