Cumulative Blast Impulse Is Predictive for Changes in Chronic Neurobehavioral Symptoms Following Low Level Blast Exposure during Military Training

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ABSTRACT

Introduction:

Cumulative low-level blast exposure during military training may be a significant occupational hazard, increasing the risk of poor long-term outcomes in brain function. US Public Law 116-92 section 717 mandates that US Department of Defense agencies document the blast exposure of each Service member to help inform later disability and health care decisions. However, which empirical measures of training blast exposure, such as the number of incidents, peak overpressure, or impulse, best inform changes in the neurobehavioral symptoms reflecting brain health have not been established.

Materials and Methods:

This study was approved by the US Army Special Operations Command, the University of North Carolina at Chapel Hill, and the VA Puget Sound Health Care System. Using methods easily deployable across different organizational structures, this study sought to identify and measure candidate risk factors related to career occupational blast exposure predictive of changes in neurobehavioral symptom burden. Blast dosimetry-symptom relationships were first evaluated in mice and then tested in a military training environment. In mice, the righting time neurobehavioral response was measured after exposure to a repetitive low-level blast paradigm modeled after Special Operations training. In the military training environment, 23 trainees enrolled in a 6-week explosive breaching training course, 13 instructors, and 10 Service member controls without blast exposure participated in the study (46 total). All participants provided weekly Neurobehavioral Symptom Inventory (NSI) surveys. Peak blast overpressure, impulse, total number of blasts, Time in Low-Level Blast Occupation, and Time in Service were analyzed by Bayesian analysis of regression modeling to determine their probability of influence on the post-training symptoms reported by participants.

Results:

We tested the hypothesis that cumulative measures of low-level blast exposure were predictive of changes in neurobehavioral symptoms. In mice, repetitive blast resulted in reduced righting times correlated with cumulative blast impulse. In Service members, peak blast overpressure, impulse, total number of blasts, Time in Low-Level Blast Occupation, and Time in Service all showed strong evidence of influence on NSI scores after blast exposure. However, only models including baseline NSI scores and cumulative blast impulse provided significant predictive value following validation.

Conclusions:

These results indicate that measures of cumulative blast impulse may have utility in predicting changes in NSI scores. Such paired dosimetry-symptom measures are expected to be an important tool in safely guiding Service members' occupational exposure and optimizing force readiness and lethality.

INTRODUCTION

Mild-to-moderate blast exposures may cause brain injury through multiple mechanisms, thereby increasing the risk of psychiatric disorders, functional impairment, and chronic neuropathology.[1–4] Less understood are the risks of low-level blast (LLB) pressures that may occur during military training, often reported in terms of peak psi (i.e., the

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maximum pressure in pounds per square inch experienced for a specific blast event) and cumulative psi (i.e., the total pressure accumulated over several blast events). While US Military training protocols have sought to limit blast peak pressures to <4 psi, Special Operations Forces (SOF) trainees and others may be exposed to cumulative and frequent overpressures, including as much as 184 cumulative psi over the course of one training week, with several months spent training each year.[5,6]

Overpressures that are <4 psi may induce tinnitus[7] and alterations of consciousness or sensation,[2,7–9] and these symptoms may worsen with repeated or chronic exposure,[2,8,9] leading to a condition consistent with US Veterans Administration, US Department of Defense, and American Congress on Rehabilitative Medicine criteria for mild traumatic brain injury (mTBI). Indeed, high cumulative exposure may contribute to increased baseline neurobehavioral symptoms in SOF members.[10–12] Together, these observations suggest that cumulative overpressure exposure may be related to changes in chronic neurobehavioral symptoms even when past exposure occurred within the <4 psi safety limit.

Animal models emphasizing clinical experiences over injury mechanisms may help improve our understanding of clinical LLB exposures. Rodent models using open-field explosive detonations[13–17] and laboratory shock tubes[18,19] often report subtle pathological and behavioral consequences of LLB over ∼2.5 to 10+ psi. Animal studies report that LLBs near ∼10+ psi often induce pathological responses in brain tissue that are accompanied by behavioral changes,[1,19–21] with both of these outcomes being consistent with well-established experimental outcomes of injurious blast-mTBI.[22–24] Conversely, animal studies examining the effects of blasts near 4 psi often report subtle effects even when using repeated LLB.[25,26] As a result, LLB animal models emphasizing injury thresholds have had poor translational performance towards informing clinical exposure-outcome relationships in LLB. Experiments better modeling the clinical experience of military units with high blast exposure may be critical in predicting the clinical outcomes of LLB and helping to define exposure limits.

We have developed a clinically relevant LLB mouse model emphasizing the heterogeneous conditions and LLB exposures experienced by SOF Service members during routine training. The model is based on our recent empirical data,[5] wherein Service members conservatively detonated 4 to 6 breaching charges per training day, which resulted in ∼17.1 to 19.4 daily cumulative psi before accounting for other implements.

The goal of this study was to first identify in mice which LLB overpressure measures predict persisting neurobehavioral change in the murine righting time (RT), a measure of arousal-based return to consciousness. Candidate measures were then tested for their performance in predicting post-acute changes in neurobehavioral symptoms as reported by SOF trainees and instructors over a 6-week breaching course.

METHODS

Animal Modeling Studies

LLB exposure in mice

Three-month-old, male C57Bl/6J mice were used with approval from the Veterans Affairs Puget Sound Health Care System Institutional Animal Care and Use Committee. Mice were group-housed, 4 to 5 to a cage, in an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)-accredited specific antigen-free (SPF) facility. Mice were maintained on a 12-hour light cycle with ad libitum food and water. Mice were subjected to either daily sham or repetitive LLB exposure for 11 consecutive work-week days using a helium-driven shocktube described elsewhere.[27] During LLB exposure, 2.5% isoflurane-anesthetized mice (1 Lpm in O_2) were positioned with their back against a rigid gurney; their wrists, ankles, and torso secured; and their ventral aspect facing the oncoming blast. Daily LLB exposure (Monday–Friday) was administered as 4 to 5 blasts (4 psi/blast; ∼20 total psi/day) occurring over ∼15 minutes for 44.8 ± 0.4 exposures (mean ± SEM) over 11 total days of exposure. The LLBs had peak pressure of 4.77 ± 0.019 psi, positive phase duration of 1.08 ± 0.005 ms, and impulse of 3.2 ± 0.005 psi•ms (mean ± SEM). Sham control mice received equal anesthesia without LLB.

Righting reflex measures in mice

Neurobehavioral assessments were performed weekly in both clinical (see below) and preclinical arms of the study. In mice, we assessed RT, a well-established measure of return to consciousness following removal from anesthesia. After the final blast/sham exposure, mice were removed from isoflurane and placed with their back onto a heated pad. RT was measured as the amount of time in seconds before mice turned over. All animals survived the duration of the study.

Clinical Studies

Participants

This study was approved by the US Army Special Operations Command and the University of North Carolina at Chapel Hill THRIVE institutional review board. Inclusion criteria for participants was specific to students enrolled in the 6-week Special Operations explosive entry (i.e., breaching) training course and their instructors. Inclusion of non-blast controls was limited to individuals who worked in the same unit without LLB exposure. There were no specific exclusion criteria. Participants could withdraw from the study at any time and provided weekly self-report Neurobehavioral Symptom Inventories (NSIs). Participant data were deidentified to reduce potential response biases. Information regarding age,

time in military service, and time in a military occupation with routine LLB exposure (i.e., time in SOF unit) was collected at study onset.

Training and blast exposure measurement

Breaching training was conducted following the standard 6-week Special Operations training protocol. LLB measures were collected from trainees and instructors using Generation 7 Blast Gauges (BlackBox Biometrics [B3], Rochester, NY) placed on the non-firing shoulder, the chest of the body armor, and the rear of the helmet. Gauge data were collected in continuous mode. The number of blast exposures, event peak psi, and impulse (psi•ms) above the 0.5 psi sensor threshold were analyzed for each participant. During training, instructors observed from catwalks elevated ∼15 feet above the training course.

Brain injury symptom measures

Neurobehavioral symptoms related to LLB exposure were assessed using the NSI,[28] a clinically validated, 22-item, self-report instrument used to measure symptom severities associated with traumatic brain injury (TBI) occurring over the previous 2 weeks, particularly vestibular (feeling dizzy, loss of balance, poor coordination), somatization (headaches, nausea, blurred vision, sensitivity to light or noise, hearing difficulty, numbness or tingling, change in taste/smell), cognitive (poor concentration, forgetfulness, indecisiveness, slowed thinking), and affective (fatigue, impaired sleep, feeling anxious or depressed, irritability, low frustration tolerance) symptom factors.[29] A baseline NSI score was established before the course started (Week 0). The final NSI survey for all study participants was conducted approximately 1 week after the last live-fire training day.

Statistical approach

All analyses were conducted in R (v3.6.1; R Core Team, Vienna, Austria). Unless otherwise noted, analysis of variance or 2-tailed unpaired *t*-tests with $\alpha = 0.05$ were used. Candidate variables explaining changes in NSI scores were evaluated by Bayesian analysis as previously described by Kruschke.[30] Bayesian modeling was used due to the highly variable clinical data and small sample size in order to reduce the risk of type I errors and leverage prior knowledge in the analysis.[31–34] In Bayesian methods, the probability of different effect values can be computed given the observed data and a prior expectation of the effect, resulting in the posterior distribution of possible parameter values.[35] We used the posterior distribution of parameters to inform conclusions regarding the probability that an effect has a specific direction and uncertainty associated with the magnitude of the effect. To interpret the posterior distribution, we evaluated effects using Probability of Direction (pd), which provides the certainty associated with the most probable effect direction (positive or negative). We next determined the effect significance using the percentage inside the Region of Practical Equivalence (ROPE). Rather than an all-or-nothing significance test, this method allows for a continuous index of significance, an essential feature to evaluate heterogeneous risk and exposure data in small group sizes. Lastly, we performed a posterior predictive check to ensure the posterior predictions accurately mimic the data. To compare different models, we computed a Bayes factor (BF) index as previously described,[36] where P(Data|Model) terms are the likelihood distribution functions, Model_1 includes candidate variables and Model_2 is the naïve intercept-only model. The Bayes factor index is computed by integrating with respect to the priors on parameters through Monte Carlo Markov Chain sampling methods:

$$BF = \frac{P(Model_1|Data)}{P(Model_2|Data)} = \frac{P(Data|Model_1)P(Model_1)}{P(Data|Model_2)P(Model_2)}$$

Using Bayes factor comparisons, we determined the performance of candidate blast variables vs. models restricted to the intercept. This provided a relative likelihood ratio of the weight of evidence provided by a particular model with the added variables. Supported candidates were then tested for predictive performance using Gibbs Monte Carlo Markov Chain sampling procedure (with 10,000 iterations) and regression analyses to determine the 95% CIs each.

Prior distributions for intercept and model error are non-informative and allow negative and positive values to be tested throughout reasonable possibilities, while priors for NSI baseline and cumulative impulse parameters are informed by prior research. The NSI baseline prior is normally distributed about 1 as N(1,2), since this should hold relatively constant over time, while the cumulative impulse prior is small and positive as N(0.5,0.25), which still allows for negative values to occur. ROPE intervals for the parameters were chosen to be intervals around zero, within which we would say the parameters are practically equivalent to no effect. The ROPE for cumulative impulse blast exposure was based upon the median cumulative impulse at each week, such that a parameter value causing increased NSI symptoms over one would be considered outside the ROPE. For example, in Week 5, the ROPE is [–0.0097, 0.0097] because at Week 5, median cumulative impulse was 103.56 psi•ms, yielding $0.0097 \bullet 103.56 = 1$. Thus, any parameter values at or greater than 0.0097 would yield a median post-training NSI increase of 1 or greater in the model, which we considered a significant effect. We would consider any coefficient estimate within these ROPE bounds to be insignificant. Similarly, in Week 6, the ROPE is [–0.0063, 0.0063] because at Week 6, median cumulative impulse was 158.73 psi•ms, yielding $0.0063 \bullet 158.73 = 1$.

RESULTS

Repetitive Blast Exposure near 4 Psi Induces Lasting Neurobehavioral Change in Mice

To examine whether highly repetitive LLB exposure is sufficient to cause predictable and persistent changes in neu-

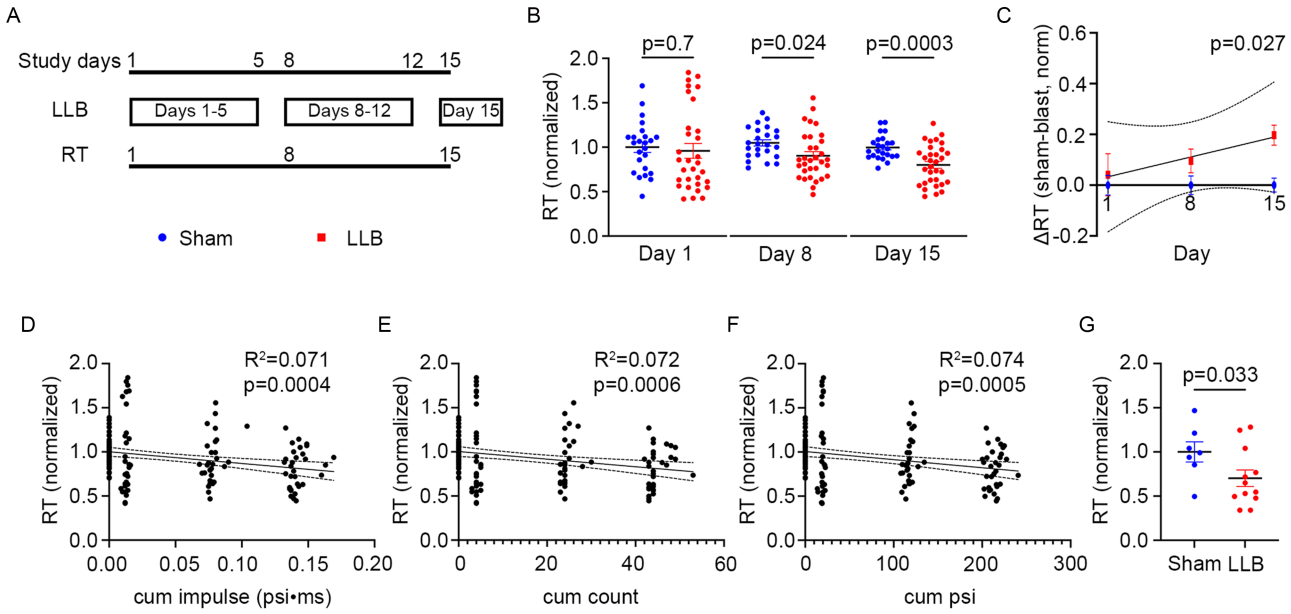

FIGURE 1. Cumulative LLB alters neurobehavioral responses in mice. (A) Experimental sequence for low-level blast (LLB) exposure and righting time (RT) measures in mice. (B) RT measures on study days (normalized to sham values). Dots represent individual mice (N= 24 Sham, 32 LLB). (C) Change in RT across study time points. Linear regression modeling of changes in normalized RT predicted by (D) cumulative impulse measured as pounds per square inch • milliseconds (psi•ms), (E) cumulative number of overpressures experienced (count), and (F) cumulative pounds per square inch (psi) of blast overpressure. (G) Normalized RTs following 5 minutes of isoflurane anesthesia in a separate cohort of mice 6 months after LLB exposure. 1-tailed t-test.

robehavioral symptoms in the absence of previous TBIs, occupational stress, or other potential confounding variables inherent in military populations, we examined the RT in an experimental LLB mouse model. The experimental sequence is illustrated in Fig. 1A. The mean RT measured after the first day of LLB exposure was unchanged when compared to RT durations in sham control animals (mean $\pm$ SEM, 1.0 ± 0.06 vs. 0.96 ± 0.08, $N = 24$ Sham mice, 32 LLB mice, $P = 0.7$, Fig. 1B), though response variability was significantly increased ($F[30,24] = 2.545$, $P = 0.024$). Continued LLB exposure was associated with reduced RT on Days 8 (1.0 ± 0.04 vs. 0.90 ± 0.05 norm RT, $N = 24$ Sham, 32 LLB; $P = 0.024$) and 15 (1.0 ± 0.028 vs. 0.80 ± 0.04 norm RT, $N = 24$ Sham, 32 LLB, $P = 0.0003$), following 1 and 2 weeks of LLB exposure (Fig. 1B). An analysis of variance similarly indicated LLB altered the RT response variability measured on both days (Day 8: $F[31, 23] = 2.34$, $P = 0.034$; Day 15: $F[31, 23] = 2.654$, $P = 0.018$). Mean differences between RT durations in sham and LLB mice increased across surveys ($F[1,2] = 34.9$, $P = 0.023$; Fig. 1C), with normalized RT durations significantly predicted by cumulative blast impulse in univariate linear regression models ($F[1, 157] = 11.98$, $P = 0.0007$, $R^2 = 0.071$; Fig. 1D). Measures of cumulative numbers of blast exposures and cumulative psi were also significantly associated with normalized RT (respectively, cumulative count: $F[1,157] = 12.19$, $P = 0.0006$, $R^2 = 0.072$; cum psi: $F[1,157] = 12.63$, $P = 0.0005$, $R^2 = 0.074$; Fig 1E, F, respectively). Lastly, to evaluate the persistence of RT changes induced by previous LLB exposure, we measured RT following a brief 5 minute anesthetic-induced loss of consciousness in mice 6 months after the final LLB/sham exposures. Compared to sham control mice, mice with previous LLB exposure demonstrated significantly chronically reduced RTs ($t[11, 6] = 1.159$, 1-tailed based on results from earlier time points, Fig. 1G). Given the low, yet significant, regression coefficients of determination and persistence of effects, these results indicate that LLB is sufficient to alter neurobehavioral responses in a manner dependent on highly repetitive exposure such as that characteristic of professional military training units, suggesting that subjects with the highest exposure are at greatest risk.

Service member Characteristics

To examine the relationship between environmental LLB exposure and changes in neurobehavioral symptom burdens, we examined a cohort of 23 Special Operations breaching trainees, 13 Special Operations breaching instructors, and 10 Service member Controls without occupational LLB exposure. All participants were male due to no females being enrolled in the studied cohort. Age of participants was 35.7 ± 0.8 years (mean $\pm$ SEM; range, 28 to 53 years). Instructors were significantly older (41.75 ± 1.19 years) and had longer time in occupations with frequent LLB exposure (time in low-level blast occupation [TILLBO]: 12.6 ± 0.99 years) compared to both control (age: 33.2 ± 1.45, years, TILLBO: 0 ± 0 years) and

trainee groups (age: 33.5 ± 0.72 years, TILLBO: 1.18 ± 0.08) (mean ± SEM).

Blast Exposure Measurements

Trainees were not exposed to live-fire explosive use until Week 3 and experienced increasing exposure during Weeks 4 and 5, with Week 5 culminating in the highest amount of measured blast exposure. Blast exposures across participants are summarized in Table I. Figure 2A illustrates the study timeline and an example of the blast exposure distribution. The exposure profiles of instructors and trainees are shown in Fig. 2B. The mean number of blast exposures among trainees was 115.6 exposures (range 1–230), with mean peak pressure 1.256 (range 1.02–5.33) psi and mean impulse 1.406

TABLE I. Summary Statistics for Blasts Measured during the Study

		Peak pressure (psi)			Impulse (psi•msec)		
	Number of blasts	Cum.	Average per blast	Max per subject	Cum.	Average per blast	Max per subject
Minimum	1	1.02	1.02	1.02	0.58	0.58	0.58
First quartile	56	87.88	1.114	2.54	119.64	1.011	4.5
Median	134	167.78	1.209	2.97	158.28	1.161	5.08
Mean	115.6	140.94	1.256	3.124	134.18	1.406	6.972
Third quartile	175	202.96	1.259	3.7	192.67	1.525	5.95
Maximum	230	259.2	1.785	5.33	258.64	3.41	28.43

Abbreviations: cum., cumulative; msec, milliseconds; psi, pounds per square inch.

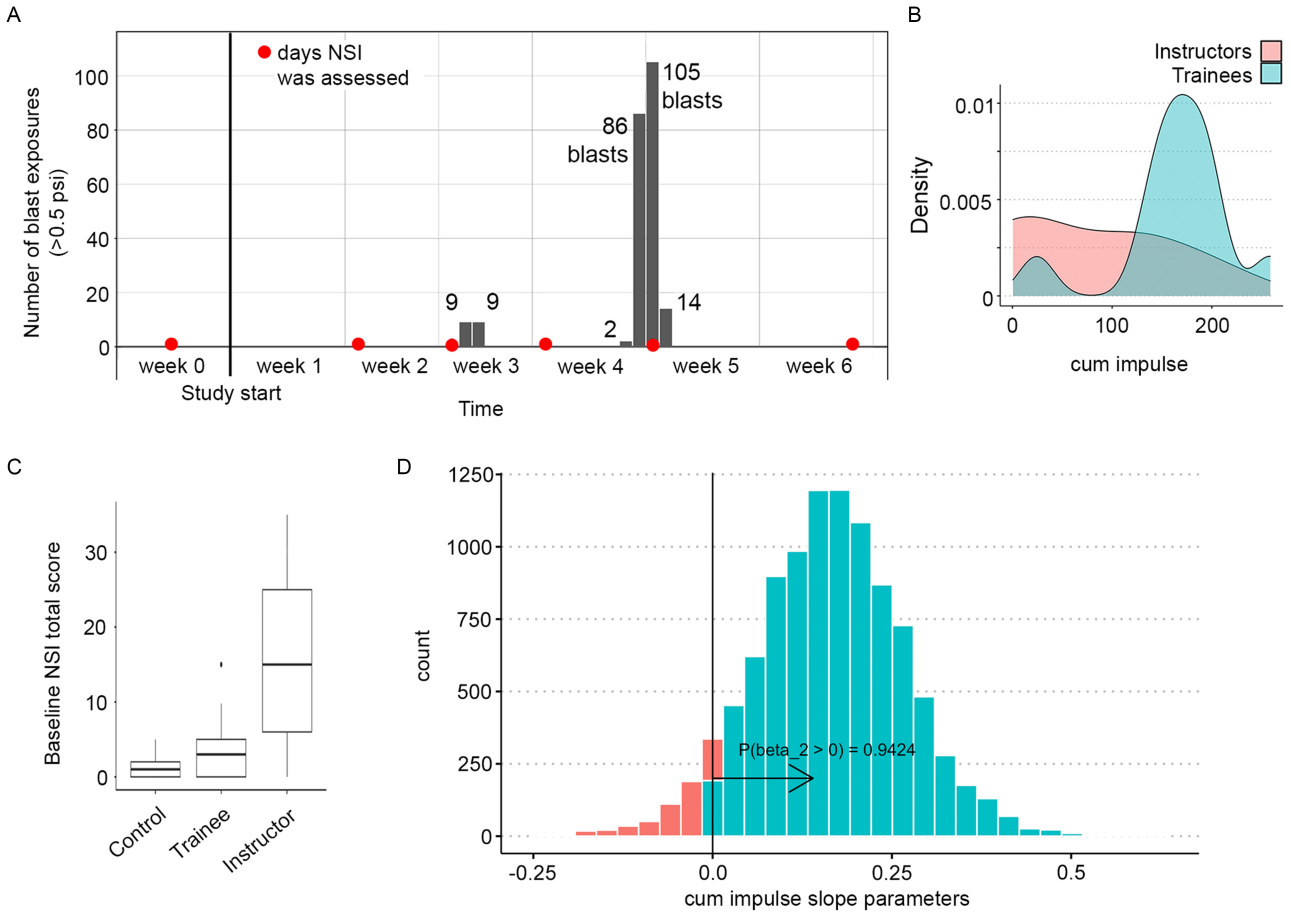

FIGURE 2. NSI and Blast Exposure Timeline (example blast data). (A) Distribution of blast exposures (Y-axis) across the study days (x-axis; Monday–Friday) from a single representative trainee. Neurobehavioral Symptom Inventory (NSI) surveys were collected as noted (red dots). No training occurred on weekends. (B) Graph represents the distribution range of cumulative impulse (pounds per square inch • milliseconds [psi•ms]) experienced by trainees and instructors during the study. (C) NSI total scores (mean ± SEM) at Week 0 for each study group. (D) The resulting posterior probability reporting the probability of increased NSI scores post-training; accounting for baseline NSI scores and cumulative impulse measured by B3 blast gauge.

(range 0.58–28.43) psi•ms, as recorded by B3 Blast gauges. Flash bang grenades and single strand detonation cord door-breaching charges accounted for 63 (40.2%) and 109 (59.8%) events over 5 days of recorded charge counts, with the order of use varying.

Neurobehavioral Symptom Measurements

Neurobehavioral symptom measures at baseline (Week 0) and during the course of the study were collected using the NSI. NSIs completed in Weeks 1 through 3 were conducted prior to any explosive training, which occurred during Weeks 4 to 6. There were statistically significant groupwise differences between baseline NSI scores of control, trainee, and instructor groups, which had factored-symptom total scores of 1.30 ± 1.49, 3.21 ± 3.65, and 15.82 ± 11.29 (mean $\pm$ SD), respectively (Fig. 2C), indicating instructors endorsed significantly greater neurobehavioral symptom burdens at baseline. After live-fire training, the NSI Affective and Somatization factors were unaffected by blast exposure in all groups under these conditions. However, there were non-significant trending differences in the Cognitive and Vestibular factors for instructors before and after Week 4 (data not shown). Cognitive symptom ratings showed non-significant trending reductions during the live-fire explosive training phase, while Vestibular symptoms increased during this same period. Cognitive symptoms were the most prominently elevated factor among NSI baseline scores for instructors; whereas, Vestibular symptoms were nearly absent. The potential confounding variables, depression and anxiety, are assessed in the NSI. Importantly, these variables were not significantly different among groups before or after blast training.

Cumulative Blast Impulse Predicts Changes in NSI Scores

Bayesian analysis of regression models was used to identify risk factors of career occupational blast exposure predictive of changes in neurobehavioral symptom burden. The most notable changes in neurobehavioral symptoms assessed by the NSI occurred during Week 5—the most intense period of LLB exposure, during which breaching charges and flash bangs accounted for an average of 115.6 blast exposures per trainee within a period of 4 days. Week 6 similarly includes NSI ratings related to blast exposure as the NSI questionnaire evaluates symptoms over the previous 2 weeks, which included the final days of explosive use.

We hypothesized that baseline NSI, TILLBO, and total Time in Service (TIS) are proxies for previous blast exposure and or other brain trauma. Thus, we used these measures as independent variables in the Bayesian modeling analysis. Cumulative peak pressure (psi), cumulative impulse (psi•ms), and total number of blasts experienced were included in the models as independent variables. The dependent variable was the sum of post-training NSI symptom ratings.

TABLE II. Bayes Factor Results for Regression Analysis

Model	Bayes factor	Evidence strength
baseline_ratings	132.3273 ±0.01%	Very strong evidence
baseline_ratings + TILLBO	33.34939 ±0%	Very strong evidence
baseline_ratings + cumulative impulse	17.78413 ±0%	Strong evidence
baseline_ratings + TIS	17.24108 ±0%	Strong evidence
baseline_ratings + number of blasts	15.62426 ±0%	Strong evidence
baseline_ratings + TIS + TILLBO	10.16583 ±0%	Strong evidence

Abbreviations: TILLBO, time in low-level blast occupation; TIS, time in service.

According to the Bayes Factor analysis of regression models, two-variable models that include a participant's baseline ratings with any one of the remaining independent variables (TILLBO, TIS, cumulative blast impulse, and total number of blasts) showed strong evidence of influence on their post-training symptoms. These results are summarized in Table II. When these models were simulated through a Monte Carlo Markov Chain (MCMC) model fitting and simulation procedure, the model with clear posterior predictive validation included only baseline NSI symptoms and cumulative blast impulse. The equation for the multi-linear regression model is

$$\hat{y}_{PostTrainingNSI} = \beta_0 + \beta_1 x_{baselineNSI} + \beta_2 x_{cu\ impulse}$$

where $y \sim N(\hat{y},\ s)$

Prior distributions for Bayesian inference of the model were

$$\beta_0 \sim N(0,10);\ \beta_1 \sim N(1,2);$$
$$\beta_2 \sim N(0.5,0.25);\ s \sim U(0,10)$$

Using non-informative priors on intercept and error parameters and informed priors on Baseline NSI and cumulative impulse parameters, the posterior distributions of model parameters were simulated and fit during typical Bayesian regression analyses as described by Kruschke.[30] For Week 5 NSI and blast data, Bayesian regression analysis yielded an R^2_{ADJ} 95% highest density interval (HDI) of (0.74, 1.0). Baseline NSI ratings had a positive effect with a 95% HDI of (0.836, 1.23). Cumulative impulse had strong credibility for a positive effect, with a 95% HDI of (−0.0270, 0.0460) and a probability of 0.708 that the coefficient for cumulative impulse effect is positive. The percentage inside the ROPE for cumulative impulse was 23.8%, indicating that impulse does not lend credible evidence to its relationship with NSI ratings following the few blast exposures occurring during Week

5. Posterior predictive checks identified no systemic discrepancies between our observed data and the simulated model data.[30]

We similarly used non-informative priors on parameters to generate the posterior distributions from Week 6. The validated model yielded an R^2_{ADJ} 95% HDI of (0.751, 1.00). Baseline NSI ratings have nearly certain positive effect with a 95% HDI of (0.785, 1.186). The probability that cumulative impulse from blast exposure has a positive effect on NSI symptoms is 0.942 with a 95% HDI of (−.042, 0.371) (Fig. 2D). The percentage inside the ROPE for cumulative impulse was 1.34%, indicating that Week 6 impulse shows credible evidence to its relationship with NSI ratings. Taken together, these results indicate that cumulative LLB impulses provoke greater changes in NSI scores relative to baseline NSI ratings, suggesting a probable interaction between continued blast exposure and aggravation of underlying and unresolved baseline injuries that may accrue over a military career.

DISCUSSION

It is unknown whether specific properties of blast overpressure would be useful for predicting neurobehavioral symptom changes after LLB exposure. We leveraged an experimental LLB mouse model to examine dosimetry-symptom relationships that may inform injuries related to military blast exposure. An essential feature of this mouse model is its highly characterized nature—minimizing blast exposure variability, controlling recovery and diet, and relative freedom from stressors such as operational tempo or classical posttraumatic stress disorder. Under these controlled conditions, by 2 weeks of modeled LLB exposure, LLB mice regained consciousness after anesthesia faster than sham control mice in a manner correlated with cumulative measures of blast impulse. RT reductions persisted at least 6 months after LLB. Though an investigation of the mechanisms underlying these phenomena are beyond the scope of the current report, persistently elevated arousal seen as lower RT would indicate a heightened sympathetic tone which is necessary to prevent syncope after blast and is highly implicated in the development of posttraumatic stress disorder, a common comorbidity of mild-to-moderate blast exposure.[37,38] Heightened arousal responses are expected to be adaptive, especially in the case of professional breachers, who must condition themselves to effectively engage combatants when they themselves are affected by breaching charges. Taken together, these experimental results demonstrate that highly repetitive LLB is sufficient to cause persistent reductions in the return to consciousness in the absence of common confounding factors.

To test these relationships in breaching naïve vs. experienced breachers, we deployed the NSI within a high-tempo training environment to capture weekly changes in self-reported neurobehavioral symptoms following highly repetitive blast exposures under 4 psi. Among many estimates of career blast exposure, we found that blast gauges worn by Special Operations Forces participants during a short training course were able to record blast dosimetry information and establish their relationship with subtle changes in NSI scores reflective of subconcussive TBI. Variables that demonstrated evidence of non-zero posterior influence on post-training NSI included number of blasts, average impulse per charge, and average psi per charge. However, only models including baseline NSI symptoms and cumulative training blast impulse retained significance upon further validation. It is important to note that B3 sensors may fail to record lower psi events,[39] indicating the current cumulative exposure estimates are likely conservative, with actual exposures being higher. Together, these data suggest that surveillance of chronic blast effects will require baseline neurobehavioral symptom measures in addition to blast exposure records including impulse, in order to guide medical decision-making and meet the intent of US Public Law 116-92 section 717 to inform Service member blast risks.

Our results indicated that trainees were not the primary at-risk group, but rather instructors were at greatest risk as predicted by the experimental mouse model data. In mice, we demonstrated a low, but significant coefficient of determination between changes in RT and cumulative blast measures indicating extensive cumulative LLB exposure may be necessary to provoke clinical neurobehavioral symptom changes. This change persisted at least 6 months after LLB in mice. In keeping with this, we only detected significant dosimetry-response relationships in breaching instructors with considerable career LLB exposure. Breaching instructors had elevated baseline and post-training NSI scores for multiple persistent post-concussive symptoms including headaches, hearing difficulty, numbness or tingling, poor concentration, forgetfulness, slowed thinking, difficulty sleeping, and irritability. Special Operations instructors are often drawn from SOF. As SOF are frequently deployed and injured during operations, this virtually ensured that each participant in the present study had a probable history of mTBI with or without loss of consciousness. Though we were unable to assess these variables in the current study, in our recent cross-sectional study of 104 asymptomatic SOF combat soldiers, 53% reported one or more mTBIs (interquartile range = 3 [2.5]) with 15%, 15%, and 70%, respectively, occurring within the last month, year, or longer.[40] These data suggest that higher instructor scores for these persistent post-concussive symptoms may relate to either or both an aggravation of previous injuries or a loss of resiliency to the effects of blast exposure.

This study has several limitations. Differences in blast exposure profiles between mice and Service members limit cross-interpolating the study data. Mice experienced a higher peak pressure (4 psi/blast) and more frequent exposure to ∼4 psi blasts (4–5 blasts per day over 15 minutes) compared to the human subjects, whose median blast exposure in Week 4 of 6 was ∼1 psi with a median 134 blasts. As our mouse model was based on empirical measures of professional SOF breachers during Close Quarter Battle (CQB) training,[5] it may better represent the experience of instructors; who were

often former professional breachers. The mouse model may better predict instructor outcomes because of this correspondence, and by extension, it may underperform regarding the expected effects of LLB in trainees with less exposure. Our results in mice do not evaluate causative molecular mechanisms or the effect of blast repetitions or intervals; therefore, we cannot suggest safe exposure limits or injury mitigation strategies. While the animal study did not receive therapeutic interventions, we could not control for such interventions in the breacher study arm; however, no medical emergencies or diagnosed TBIs occurred during the study. The generalizability of the study may be limited by its small sample size and the exclusive use of SOF participants during the short 6-week training course. Our clinical blast measurements relied on field-deployable B3 blast gauges. Though the Department of Defense's development of a Blast Overpressure Tool (accessed via the Range Manager Toolkit) may provide additional aid for assessing and mitigating potential blast injuries from a number of Tier 1 weapons systems including breaches, we have found the B3 gauge as an available and effective instrument for recording personal exposures in dynamic CQB environments. It is important to note, however, that the idealized Blast Overpressure Tool is expected to predictively assess exposure for range management and training, as well as, facilitate blast exposure documentation for Service members as mandated by US Public Law 116-92 section 717; which the B3 system does not presently enable. Lastly, Bayesian statistical approaches enrich our understanding of causal relationships by incorporating prior knowledge, offering valuable insights into potential directions of causation. This framework's strength lies in its ability to adapt to the nuances of complex relationships. However, when dealing with small sample sizes, Bayesian analyses face challenges in providing precise estimates and may be sensitive to prior specifications. To ensure the accuracy and clinical relevance of the studied effects, future studies must prioritize larger sample sizes, acknowledging that increased data robustness is essential for more accurate estimations of effect size and clinical significance.

In conclusion, this study identified a potential predictive relationship between cumulative blast impulse and changes in neurobehavioral symptoms. Though a simple linear relationship between them was experimentally established in mice, we found that the blast dosimetry-outcome relationships were best informed when accounting for both baseline neurobehavioral symptoms and cumulative blast impulse in humans. These data indicate that Service members with greater preexisting symptom burdens may experience worse outcomes following repetitive environmental blast exposures even when under the US Military training safety threshold of 4 psi.

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CLINICAL TRIAL REGISTRATION

Not applicable.

INSTITUTIONAL REVIEW BOARD (HUMAN SUBJECTS)

This study was approved by the US Army Special Operations Command and the University of North Carolina at Chapel Hill THRIVE institutional review board (IRB).

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC)

Animal components of this study conformed to protocols approved by the VA Puget Sound Institutional Animal Care and Use Committee.

INDIVIDUAL AUTHOR CONTRIBUTION STATEMENT

Study design: CM, AC, GM, PM, JSM, JPM. Data collection: CM, AC, GM, JSM, JPM. Analysis: CM, JC, JSM, RGT. Manuscript writing: CM, AC, JC, RAI, JSM. Funding: JSM. SFC McEvoy and Crabtree are Co-First Authors.

INSTITUTIONAL CLEARANCE

Not required as confirmed by institution.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they do not have competing or conflicting interests.

DATA AVAILABILITY

Data used in this report are available upon reasonable written request to the corresponding author.

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