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Repeated Low-Level Blast Exposure: A Descriptive Human Subjects Study

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ABSTRACT The relationship between repeated exposure to blast overpressure and neurological function was examined in the context of breacher training at the U.S. Marine Corps Weapons Training Battalion Dynamic Entry School. During this training, Students are taught to apply explosive charges to achieve rapid ingress into secured buildings. For this study, both Students and Instructors participated in neurobehavioral testing, blood toxin screening, vestibular/auditory testing, and neuroimaging. Volunteers wore instrumentation during training to allow correlation of human response measurements and blast overpressure exposure. The key findings of this study were from high-memory demand tasks and were limited to the Instructors. Specific tests showing blast-related mean differences were California Verbal Learning Test II, Automated Neuropsychological Assessment Metrics subtests (Match-to-Sample, Code Substitution Delayed), and Delayed Matching-to-Sample 10-second delay condition. Importantly, apparent deficits were paralleled with functional magnetic resonance imaging using the n-back task. The findings of this study are suggestive, but not conclusive, owing to small sample size and effect. The observed changes yield descriptive evidence for potential neurological alterations in the subset of individuals with occupational history of repetitive blast exposure. This is the first study to integrate subject instrumentation for measurement of individual blast pressure exposure, neurocognitive testing, and neuroimaging.

INTRODUCTION

The relation between primary blast exposure and traumatic brain injury (TBI) is not well understood and remains controversial. Approaches used to explore this connection include experimental animal models and human surrogates. Both are limited by the requirement for appropriate scaling to relate observations to human real world blast scenarios and to the clinical setting. The generalizability of experimental observations is of particular importance when determining whether blast exposure can cause cognitive dysfunction in humans without evidence of injury on either clinical examination or conventional neuroimaging.

To investigate whether repeated exposures to low-level blast events are associated with alterations in neurocognitive function or neuroimaging in an exposed human population, a population of breachers was identified at the U.S. Marine Corps Weapons Training Battalion (WTB) Dynamic Entry School (DES). Breachers are a unique population who, as part of their regular training, are exposed to series of controlled blasts under supervised conditions that minimize the risk of injury from debris, fragments, or whole-body translation. Breachers participating in DES training are shown in Figure 1.

Breaching is the practice of using a variety of methods to gain entry to secured structures. Methods range from lock picking to controlled use of explosives. Explosive breaching was the focus of this investigation. Because blast exposure is controlled during breaching, the effects from a single exposure to blast overpressure do not result in an injury event that would prompt immediate concussion screening. Safety measures in place include use of safe standoff distances and hearing protection. However, anecdotal reports of neurological symptoms in experienced military and law enforcement breachers have emerged. Those anecdotal reports are echoed in a recent survey of symptoms among this population.[1]

The symptoms reported in this population include headaches, sleep disturbances, and working memory impairment and are similar to those reported by service members with

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FIGURE 1. During breaching exercises participants used charges ranging from 0.03 to 5 pounds (net explosive weight) to gain entry to a variety of structures.

mild TBI who also report greater numbers of blast exposures.[2] Among breachers, symptoms are more frequently reported by experienced personnel and are temporally correlated with periods of active field explosive training. Of note, such experienced personnel are those who become breaching Instructors and thus participate in multiple courses throughout the year and, by virtue of their job description, are routinely exposed to low-level blast. The tendency for symptoms to be reported by experienced breachers has raised the question as to whether cumulative injury may occur following repetitive exposure to low-level blast. To date, studies addressing this question of effects in humans from breaching blast have been equivocal, yielding no supporting evidence[3,4] or evidence for isolated effects.[5]

The scientific objective of this study was to determine whether measureable changes in neurological function, as assessed through behavioral and neuroimaging examinations, are associated with the repeated low-level blast exposures that occur as part of standard breacher training. At the outset, the working hypothesis that primary blast exposure can cause cumulative neurological injury included an expectation that such changes would be small. A measurable effect yielding conventional evidence of serious injury would have been recorded by training command personnel during routine operations and would have been prevented from recurrence through revision in procedures. However, a small effect or subclinical injury, developing slowly over repeated exposures and manifested to differing degrees amongst a group of individuals, might escape notice. As such, capture of a signal associated with a slowly developing, smaller effect might only be possible through targeted objective measurements.

METHODS

This study was approved by the Institutional Review Boards of the Naval Medical Research Center and the University of Virginia (UVA) in compliance with all applicable Federal regulations governing the protection of human subjects. The study was conducted with two separate 2-week breacher basic training courses at the WTB/DES in Quantico, Virginia.

During the breacher basic course, the first 2 weekdays are classroom-based, the next 6 weekdays are breaching practicum, and the last 2 weekdays are for administrative tasks (Fig. 2). The intervening weekend days are liberty days, with no structured activities scheduled so as to leave time for the Students to review coursework. For the study reported here, the weekend days before and after the course, and a 30-minute period at the end of every training day, were dedicated to subject evaluations specific to the research protocol.

Participants underwent neurobehavioral testing, blood toxin screening, vestibular and auditory testing, and neuroimaging during the weekends before and after the 2-week training course. The first weekend provided a baseline condition for the test subjects, against which the post-exposure results could be compared. Computerized neurobehavioral testing and limited vestibular/auditory assessments were performed during the training period, thus facilitating the detection of acute neurological and auditory changes. To correlate human response measurements and the blast loading environment, participants were instrumented with pressure gauges.

Subjects

The subjects studied consisted of 40 research volunteers who were the U.S. Marines in one of three study groups: Students, Instructors, or Controls. Students ($n = 28$) were those enrolled in the breacher basic course. Instructors ($n = 5$) were those who taught DES breaching courses. Controls ($n = 7$) were recruited from Marine Corps Base Quantico, but were not connected to the breacher basic course and not exposed to blast during the period of the study. Of the 28 Students, 26 completed the training course. The two Students who did not complete the course were not included in the final analysis. Another Student was excluded from the analyses because of medical issues unrelated to this protocol, yielding a total of 25 subjects for the Student group in the final analysis. Baseline evaluations of the Control subjects revealed that five of the seven were below the range presented by the 30 blast-exposed subjects and, thus, were not equivalent to the experimental groups; for this reason, none of the Control subject results are presented.

Among those included in the analyses, the mean age and education for Students and Instructors were similar (26 and 28 years old, respectively, and between 12 and 13 years of education for both groups). Ethnicity/race was predominantly Caucasian (27 of 30) with English as the self-reported native language for all. All subjects were right handed. Subjects provided histories indicating prior blast exposures ranging

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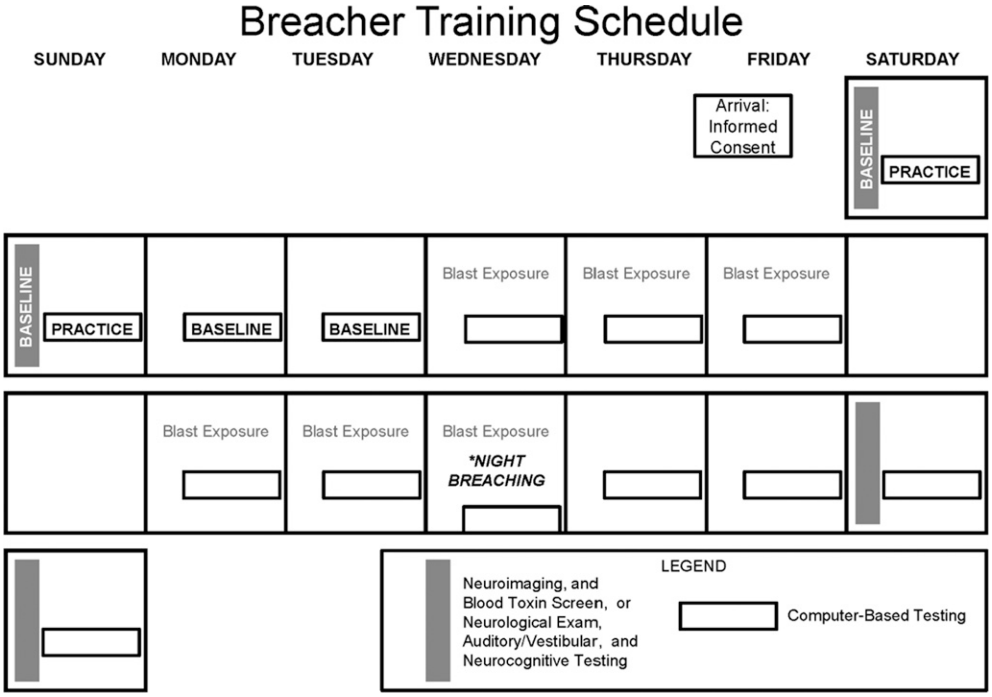

FIGURE 2. Breacher training schedule during which volunteers also participated in neurocognitive testing, blood toxin screening vestibular/auditory testing and neuroimaging.

from 0 to 700 blasts. Only two of the subjects in the study were blast naive before entering the study.

Criteria for magnetic field safety were applied separately to the 30 subjects and are described in the Neuroimaging section, as those criteria affect only the neuroimaging data.

Blast Characterization

The predominant blast components responsible for the neurological sequelae of mild blast-induced TBI are unknown, but blast overpressure is largely accepted as an important traumatic mechanism given that up to 90% of the energies released on detonation of an uncased charge are converted into the formation of the shock wave.[6] As such, breacher Students and Instructors were each instrumented with 4 pressure gauges (on their helmets above each ear and on each shoulder) and a 3 degree-of-freedom inertial cube (on the apex of their helmets). Blast exposures were further characterized using a free-field pressure gauge placed in the vicinity of each group of breachers to provide a reference data point. Sensor data were recorded at a rate of one million samples per second after passing through a 200 kHz antialiasing filter. The data were stored electronically for postprocessing.

Neurocognitive/Neuropsychological Evaluation

As a starting point, we conducted a review of the subjects' medical records for information related to history of head injury or neurological impairment. In conjunction with this medical record review, all subjects were examined by a board-certified neurologist for signs of neurological abnormality, inclusive of mental status, cranial nerve function, motor strength, sensation, coordination, deep tendon reflexes, and gait. The neurocognitive assessments that followed consisted of technician-administered measures, self-report inventories, and computer-based cognitive performance measures. The assessments selected for this study (Table I) were based on a review of head injury literature and were intended to reveal and quantify changes in specific neurocognitive domains.

Technician-Administered and Self-Report Neuropsychological Measures

Technician-administered measures were conducted with each subject on an individual basis and completed in approximately 2 hours. The order of these measures was counterbalanced across subjects and held constant within subject from pre-exposure to post-exposure. Alternate forms of measures were used for pre-exposure and post-exposure when appropriate. On completion of the session, the test administrator provided the subject with self-report inventories and left the room. Subjects turned in the completed self-report inventories to a central location.

Computer-Based Neuropsychological Measures

Computer-based testing was administered 13 times to the subjects throughout the 2-week course, at the end of each training day. During each group testing session, subjects completed two different computerized batteries: the Automated Neuropsychological Assessment Metrics (ANAM) TBI Battery[7] and a modified version of the Delayed Matching-to-Sample

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TABLE I. Neuropsychological Test Library

Technician Administered	Computer Based
Trails A and B	ANAM TBI Battery
Controlled Oral Word Association Test	Mood Affect Score
	Stanford Sleepiness Scale
California Verbal Learning Test II	Simple Reaction Time
	Code Substitution
Weschler Adult Intelligence Scale-III Subtests	Code Substitution Delayed
	Procedural Reaction Time
Digit-Symbol Coding	Match-to-Sample
Symbol Search	Mathematical Processing
Digit Span	Delayed Matching-to-Sample
Letter-Number Sequencing	
Wechsler Test of Adult Reading	
Test of Memory Malingering	
Self-Reported Symptoms	
Beck Depression Inventory-II	
State-Trait Anxiety Inventory	
Self-Report Blast Exposure	
Post-traumatic Stress Disorder Checklist-Military Version	

(DMTS) test.[8] These batteries were always completed in the order listed and the combined testing was completed in approximately 23 minutes. Each of these tests, ANAM and DMTS, is designed for repeated administration, varying test stimuli in a controlled manner between sessions.

The ANAM TBI Battery subtests assess different cognitive abilities (Table I) and are selected to be sensitive to effects of brain injury.[7,9] ANAM subtests in general involve visually presented stimuli and computer mouse responses. Responses are recorded by the computer and scored for accuracy and response time. Instructions to subjects are to be both "fast and accurate."

The DMTS assessment is a separate software application than the ANAM TBI Battery. The test paradigm is similar to the ANAM Match-to-Sample (M2S) subtest with two key differences: (1) DMTS stimuli are more complicated than M2S stimuli (8 × 8 matrix vs. 4 × 4 matrix, respectively) and (2) DMTS trials had a variable interstimulus delay (1 second or 10 seconds) instead of the static 5-second delay in M2S. The additional level of complexity in the DMTS served as an additional assessment of working memory, to mitigate potential ceiling effects in ANAM M2S. The variable interstimulus delay in DMTS means that there are 4 scores: accuracy and response time scores for the 1-second delay (easier condition) and accuracy and response time scores for the 10-second delay (harder condition). DMTS has demonstrated sensitivity to detect impairment of working memory in a field situation with operational personnel.[8,10]

Neuroimaging

Magnetic resonance imaging (MRI) was used as the imaging modality for this study. Subjects underwent MRI safety screening per standard UVA health system clinical protocol. Subjects who failed the safety questionnaire were excluded from the neuroimaging portion of the study. Of the 25 Students and the 5 Instructors, 5 Students and 1 Instructor were excluded from MRI procedures because of the possibility of metal in the region of the head. One Student's late arrival to the training course precluded his travel to UVA for MRI at pretest and he was excluded from the MRI data set. In sum, 19 Students and 4 Instructors were included in the MRI procedures and analyses.

MRI examinations included blood oxygen level-dependent (BOLD) sequences, acquired during the conduct of within-scanner tasks for functional magnetic resonance imaging (fMRI), diffusion weighted imaging across multiple vectors for diffusion tensor imaging, T1-weighted, T2-weighted, fluid attenuation inversion recovery, and susceptibility weighted imaging sequences. The objective of the current communication is to examine measureable changes in neurological function, and as such, this article provides descriptions of the fMRI data only. Structural neuroimaging will be reported separately.

For fMRI, n-back working memory and sentence completion language comprehension/word generation tasks were employed. For both tasks, stimulus presentation and response delivery were performed using the Eloquence fMRI system (Invivo, Orlando, Florida), consisting of a liquid-crystal display screen integrated into the head coil and a keypad for subjects' responses. The n-back task was chosen based on anecdotal reports from breacher Instructors of working memory difficulties and on multiple reports in the literature describing the utility of this task in the characterization of mild TBI.[11–13] The sentence completion task was chosen based on anecdotal reports from breacher Instructors of word finding difficulties and from members of the research team who reported observations of characteristic word finding deficits in patients with mild TBI associated with blast exposure. Each task consisted of five alternating 30-second baseline and activation epochs for a total of 5 minutes per run and runs were repeated three times. The n-back task involved serial presentation of letters and subject recognition of a target letter presented two letters previously (2-back condition). The sentence completion task involved observation of a coherent sentence with a blank and subjects were asked to covertly think of the appropriate word to substitute for the blank. All subjects received task training on a separate computer workstation just before entering the scanner.

Images were acquired with repeated single-shot echo-planar imaging: echo time = 30 ms, flip angle = 90°, matrix = 64 × 64, field of view 192 × 192 mm^2, slice thickness = 3.0 mm, repetition time = 3,000 ms, and 36 slices. A three-dimensional magnetization-prepared rapid acquisition with gradient echo T1-weighted isotropic whole brain data set was acquired for detailed anatomical correlation: repetition time = 1,900 ms, echo time = 1.89 ms, flip angle = 9°, matrix = 256 × 256, slice thickness = 1 mm, and 192 sagittal slices with no gap. All magnetic resonance images were collected using a 3T Siemens Trio scanner (Siemens AG,

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Erlangen, Germany) located within the MRI department of the UVA Health System (Charlottesville, Virginia).

Data analysis was performed using BrainVoyager 1.10 (Brain Innovation, Masstricht, The Netherlands) in a fashion similar to that described by Dricot et al.[14] Thresholds of at least $t > 2.87$ (one-tailed, p [Bonf] <0.01) with q (false discovery rate) <0.05 were utilized. Differing thresholds were employed to adjust for anatomically meaningless clusters of activation. Regions of significance were defined based on clusters of activation observed within the statistical map generated from a two-factor repeated analysis of variance (ANOVA).

Other Evaluations

Other evaluations in this study included serum-based lead toxicity assessments and environment lead measurements, to address potential confounding effects associated with the use of lead-cased charges at the WTB/DES training site. Audiology and vestibular measures were assessed as well. Measured lead levels were well below the Occupational Safety and Health Administration permissible limit of 50 $\mu g/m^3$. Audiology and vestibular findings from this study were communicated elsewhere.[15]

Analysis

The planned between subjects comparison groups were Student and Instructor. The repeated measures design afforded two separate within subjects evaluations of change associated with exposure to blast. One evaluation compared assessments conducted on the weekend days before the 2-week training to the weekend days after the 2-week training (Fig. 2, Saturday/Sunday Pre-Exposure vs. Saturday/Sunday Post-Exposure). The other evaluation used the daily administration of computer-based neuropsychological testing to compare baseline performance to performance within hours following blast exposure, rather than performance on the final day of the protocol. As such, these computer-based neuropsychological testing data may reflect transient neurological alterations not present at the time of the technician-administered, self-report, and fMRI assessments. The pressure gauge recordings among individuals were used to reveal the time point with the greatest magnitude blast exposure and, thus, the time point most likely for acute effects among the volunteers. Because these measurements were made in context of a standard military training protocol (rather than exposing humans to experimentally scripted blasts, which would not be ethical), the time point to examine acute effects was not known a priori.

The sample size available for the Instructor group was quite small ($n = 5$), limited by the inherent low density of the qualified Instructor population. Accordingly, analyses were considered descriptive in nature, useful for characterizing data from this type of study, but limited as support for reliable inference. Means were used to summarize the available data and repeated measures ANOVA was used for evaluations of blast-related change, comparing Student and Instructor groups on assessments conducted before and after exposure to blast. The analyses were planned comparisons and limited to descriptive purposes, so we did not use correction for multiple comparisons nor did we combine separate types of assessments into composite variables.

An accuracy criterion of ≥57% was applied to the ANAM TBI Battery as a subject exclusion criterion. This criterion is recommended by the software distributor and is the criterion applied in the Department of Defense use of the ANAM TBI Battery.

RESULTS

Breaching Environmental Characterization

Over the 2-week breacher training course, each subject was exposed to 40 low-level blasts. Over 4,400 pressure traces were collected, with an 80% successful data capture in Phase 1 and a 98% successful data capture in Phase 2. Sixty-one percent of the measured peak incident pressures were below 1 pound per square inch (psi); 4% were above 4 psi. The highest peak incident pressure measured on all breachers was 13.0 psi. The minimum peak incident pressure was 0.1 psi.

The variance in cumulative impulse and peak pressure day-to-day was related to the size and number of charges detonated on a particular day. The average day-to-day variance is shown in Figure 3. The greatest exposure was on day 4 of the practicum exercises (Monday of the second week) when the two largest charges of the training program were detonated. The cumulative impulse on that day represents 25 to 30% of the total exposure over the 2-week training course and was over two times larger than the exposure on any other day, verified by the total explosive material detonated on that day. If cognitive changes are related to the level of blast exposure, it would be expected that the greatest change in function should be detected on this day or shortly thereafter; thus, Day 4 of the practicum became

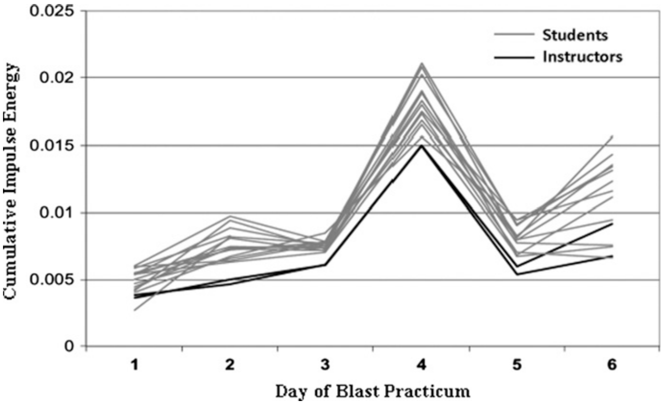

FIGURE 3. Cumulative impulse energy received each day. The greatest exposure observed occurred on day 4. On any given day, the Instructors standing at the back of the stack typically had a lower exposure level than the Students.

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the basis for our comparison of the daily computer-based neuropsychological testing.

Daily and cumulative impulse was selected as the preferable measure of an individual's overall exposure because it accommodates variables of peak pressure, duration, and pressure wave irregularities generated from being inside structures. Comparing exposures for the 2-week period using cumulative impulse, the average exposure for the Students was 0.0510 (standard deviation 0.014) psi-s compared to 0.0433 (standard deviation 0.002) psi-s for the Instructors. The standard deviation for the Student group is larger (27%) because the Students rotated among different positions in the breacher "stack," whereas exposure between Instructors was more consistent (2%) because they consistently stood at the rear of the stack. On a day-to-day basis, the Instructors consistently had the smallest exposure overall (Fig. 3).

Neurobehavioral Assessments

Baseline Neuropsychological Function

At pretest, all subjects in the Student and Instructor groups were within normal ranges on neurological examination and Post-traumatic Stress Disorder Checklist-Military Version, Beck Depression Inventory-III, and State-Trait Anxiety Inventory (STAI) measures (Table II). Wechsler Test of Adult Reading-based estimates for intelligence quotient were above 90 for all subjects and group means were 105 and 108 for Students and Instructors, respectively. All subjects met Test of Memory Malingering criteria for sufficient effort. In the computer-based testing, for each ANAM subtest, all subjects showed response times for correct responses and percentage of correct responses that were equal to or above mean performance levels for a comparable cohort.[7] There are no normative values available for the DMTS test used in this study.

Technician-Administered Neuropsychological Measures

The battery of technician-administrated neuropsychological tests before and after the 2-week training period did not show change from pre-exposure to post-exposure or showed change consistent with practice effects expected in repeated administration of tests (Tables II and III). This pattern was observed for the sample as a whole and by group. An exception to this characterization of results is California Verbal Learning Test II (CVLT II) (Table III). The CVLT II recognition accuracy (hit rate) and d' scale, a measure of sensitivity in cued recognition after long delay,[16] showed a deficit for the Instructor group at post-exposure, following blast exposure.

Self-Report Measures

The changes in symptom reporting (on the 5-point scale History and Symptoms Questionnaire[17]) between pre-exposure and post-exposure showed reporting differences among symptoms and among individuals. The symptom "Headaches" showed the greatest incidence of severity increase, with 8 of 25 (32%) Students reporting an increase and 3 of 5 (60%)

TABLE II. Neuropsychological Test Mean Scores Pre-exposure and Post-exposure

					Practice Effect		Interaction	
Measure	Pre	Post	Δ	Δ±	*F* Value	*p* Value	*F* Value	*p* Value
Stroop Interference Score					0.76	0.392	2.20	0.150
Instructor	15.29	12.81	−2.48	+				
Student	13.34	13.99	0.65	−				
Spatial Processing Simultaneous (Throughput)					0.09	0.763	0.58	0.455
Instructor	38.18	35.22	−2.96	−				
Student	38.85	40.12	1.27	+				
Spatial Processing Delayed (Throughput)					5.43	0.027	1.33	0.259
Instructor	36.20	43.78	7.58	+				
Student	41.24	43.81	2.57	+				
Post-traumatic Stress Disorder Checklist-Military Version					0.05	0.827	2.92	0.099
Instructor	28.20	23.54	−4.66	+				
Student	30.20	22.00	−7.20	+				
Beck Depression Inventory					0.01	0.933	0.01	0.933
Instructor	5.40	5.40	0.00	0.00				
Student	2.64	2.48	−0.16	+				
STAI-State Anxiety (Number and Degree of Symptoms)					5.87	0.022	0.16	0.737
Instructor	32.00	28.20	−3.80	+				
Student	30.24	25.20	−5.04	+				
STAI-Trait Anxiety (Number and Degree of Symptoms)					1.32	0.260	0.92	0.345
Instructor	29.60	29.40	−0.20	+				
Student	29.88	27.64	−2.24	+				

Computer-administered or paper-and-pencil inventory neuropsychological test mean scores at pre-exposure and at post-exposure presented by group (data columns 1 and 2, respectively; Instructor $n = 5$, Student $n = 25$). Difference between each pre-exposure–post-exposure pair of these mean scores is presented in data column 3. Column 4, "Δ±," indicates if the change value (column 3) represents an improvement (+) or a decline (−) in performance. Results of repeated measures ANOVA are presented in data columns 5 and 6 for repeated testing effect and in data columns 7 and 8 for repeated testing interaction between subject groups.

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TABLE III. Administrator-Led Neuropsychological Test Mean Scores Pre-exposure and Post-exposure

						Practice Effect		Interaction	
	Measure	Pre	Post	Δ	Δ±	*F* Value	*p* Value	*F* Value	*p* Value
Executive Function	COWA					9.00	0.006	0.68	0.415
	Instructor	43.54	49.93	6.39	+				
	Student	45.50	49.13	3.63	+				
	Animals					0.53	0.474	0.14	0.714
	Instructor	41.00	44.20	3.20	+				
	Student	44.48	45.52	1.04	+				
	Trails B					3.01	0.094	0.02	0.900
	Instructor	54.00	58.40	4.40	+				
	Student	56.92	60.72	4.20	+				
Attention/W. Memory	Digits Span					0.21	0.653	0.21	0.653
	Instructor	55.60	55.60	0.00	0.00				
	Student	51.88	53.48	1.60	+				
	Letter-Number Sequencing					5.45	0.027	1.46	0.237
	Instructor	51.40	57.20	5.80	+				
	Student	55.80	57.64	1.84	+				
Speed of Processing	Digit Symbol Coding					13.30	0.001	0.86	0.363
	Instructor	53.80	62.40	8.60	+				
	Student	55.96	61.08	5.12	+				
	Symbol Search					14.72	<0.001	0.05	0.832
	Instructor	54.40	61.20	6.80	+				
	Student	58.68	64.76	6.08	+				
	Trails A					5.08	0.032	0.19	0.665
	Instructor	56.40	60.80	4.40	+				
	Student	55.32	61.84	6.52	+				
Verbal Episodic Memory	CVLT Trial 1 Free Recall					0.22	0.647	1.38	0.250
	Instructor	47.00	49.00	2.00	+				
	Student	52.20	47.60	−4.60	−				
	CVLT Trial B Free Recall					0.55	0.464	0.55	0.464
	Instructor	44.00	44.00	0.00	0.00				
	Student	52.60	48.40	−4.20	−				
	CVLT Trials 1–5 Free Recall					0.31	0.579	1.06	0.313
	Instructor	54.60	58.00	3.40	+				
	Student	56.84	55.84	−1.00	−				
	CVLT Short Delay Free Recall					0.31	0.582	0.04	0.854
	Instructor	54.00	56.00	2.00	+				
	Student	55.20	56.20	1.00	+				
	CVLT Short Delay Cued Recognition					0.34	0.563	1.16	0.292
	Instructor	56.00	55.00	−1.00	−				
	Student	55.40	58.80	3.40	+				
	CVLT long Delay Free Recall					4.94	0.035	3.66	0.066
	Instructor	47.00	55.00	8.00	+				
	Student	55.20	55.80	0.60	+				
	CVLT Long Delay Cued Recognition					<0.01	0.965	<0.01	0.965
	Instructor	52.00	52.00	0.00	0.00				
	Student	55.00	55.20	0.20	+				
	CVLT Hit					1.84	0.186	5.69	0.024
	Instructor	50.00	42.00	−8.00	−				
	Student	49.40	51.60	2.20	+				
	CVLT False Positive					2.36	0.136	0.31	0.581
	Instructor	50.00	53.00	3.00	−				
	Student	46.80	48.20	1.40	−				
	CVLT d’					3.47	0.073	7.80	0.009
	Instructor	54.00	47.00	−7.00	−				
	Student	54.60	56.00	1.40	+				

Administrator-led neuropsychological test mean *T* scores at pre-exposure and at post-exposure presented by group (data columns 1 and 2, respectively; Instructor $n = 5$, Student $n = 25$). Difference between each pre-exposure–post-exposure pair of these mean scores is presented in data column 3. Column 4, “Δ±,” indicates if the change value (column 3) represents an improvement (+) or a decline (–) in performance. Results of repeated measures ANOVA are presented in data columns 5 and 6 for repeated testing effect (practice effect) and in data columns 7 and 8 for practice effect interaction between subject groups.

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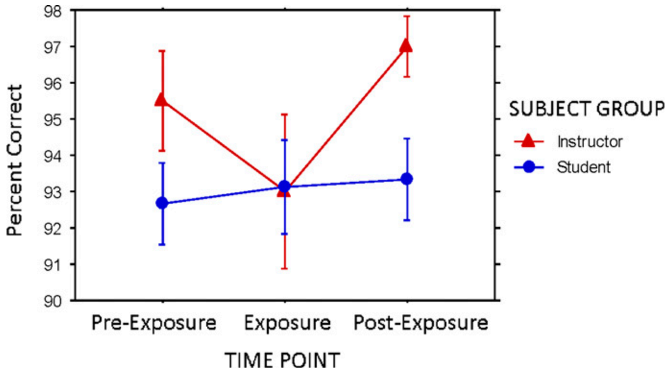

FIGURE 4. M2S Percent Correct means by 3 time points and by subject group ($n = 29$, Instructors = 5, Students = 24). Error bars are standard error. Higher points in the plot represent more accuracy in responses and better performance relative to lower points in the plot. Practice effect and interaction are nonsignificant [$F_{(2,54)} = 1.27$, $p = 0.290$, $F_{(2,54)} = 1.11$, $p = 0.337$, respectively].

Instructors reporting increase over the 2-week period. Of the remaining symptoms, no symptom was reported by more than 20% of the sample. In general, across all 22 queried symptoms, 11 of 25 (44%) Students reported increase following blast exposure as compared to 4 of 5 (80%) Instructors.

Computer-Based Neuropsychological Measures

As described in the Analysis section, a key difference between the computer-based assessments and the technician-administered neuropsychological assessments was in frequency of administration and consequent availability of data in close temporal proximity to blast exposure (<3 hours) for computer-based assessments. Computer-based performance results are reported here as three time points, characterizing (1) baseline, (2) following exposure to largest blast (day 4 of explosives practicum; see Fig. 3), and (3) 2 days after final exposure to blast. Baseline was defined as mean performance across Sessions 3 and 4 (the Monday and Tuesday of the first week of the data collection), which is before blast exposure for the course, but after Sessions 1 and 2, allowing for known practice effects.[18] Similarly, the comparison time points also represent scores from two consecutive sessions, averaged to reduce effects of day-to-day variance in performance and in consideration of the relatively small sample size. Figures 4 to 6 are group means for each of these three time points.

The 57% accuracy criterion affected 3 of the 7 ANAM subtests (Table I). Specifically, in M2S, 1 of the 30 subjects was excluded (1 Student) and in Mathematical Processing (MTH) and Code Substitution Delayed (CDD), 3 of 30 subjects were excluded (2 Students). The 1 Student removed from ANAM M2S was also 1 of the 2 Students removed from the ANAM MTH and CDD subtests. The DMTS is a much more difficult test than the ANAM subtests. In previous use of versions of DMTS with samples of military populations, the prediction was that 20 to 25% of the population find the test too difficult.[10] On the basis of DMTS developer a priori experienced-based predictions, we included all 30 subjects rather than use a 24% subject exclusion rate.

Results consistent with practice effect are reported elsewhere.[18] Primary results reported here are those that show group difference, Instructor vs. Student. Statistical power in these analyses was low, as a function of small sample size and also of the hypothesized small effect size. Mean differences reported here illustrate a pattern of responses for the Student and Instructor groups across the three time points, specifically, a pattern of Instructors' decreased accuracy observed among tasks with a memory demand and not observed among tasks without a memory demand.

As with the battery of technician-administered neuropsychological tests at pre-exposure and post-exposure, ANAM subtests Code Substitution (CDS), procedural reaction time (PRO), and MTH showed general ceiling effects for accuracy (<5% error) and a repeated administration practice effect in response time for correct responses. Simple Reaction Time (only a single choice response and thus no errors or accuracy

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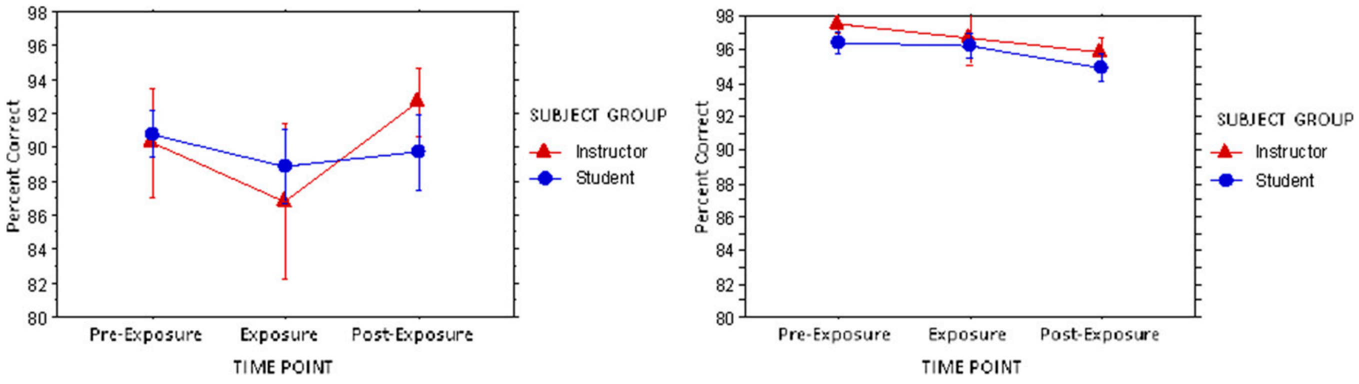

FIGURE 5. Code Substitution Delayed (CDD) Percent Correct means, by 3 response time points and by subject group ($n = 27$, Instructors = 4, Students = 23). Error bars are standard error. Higher points in the plot represent more accuracy in responses and better performance relative to lower points in the plot. For comparison, the plot on the right side is Code Substitution (CDS) Percent Correct means for the same subjects as the plot on the left. CDD has a memory burden and CDS has not. Practice effect and interaction are nonsignificant for both CDD [$F_{(2,50)} = 2.08$, $p = 0.136$, $F_{(2,50)} = 1.13$, $p = 0.332$, respectively] and CDS [$F_{(2,50)} = 2.56$, $p = 0.087$, $F_{(2,50)} = 0.12$, $p = 0.892$, respectively].

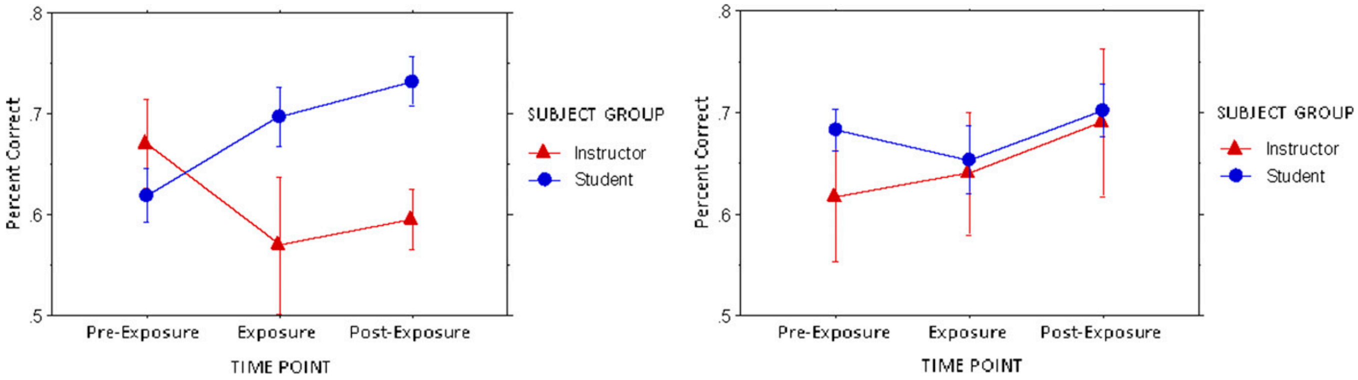

FIGURE 6. DMTS 10-Second Delay condition Percent Correct means, by 3 response time points and by subject group (n = 30, Instructors = 5, Students = 25). Error bars are standard error. Higher points in the plot represent more accuracy in responses and better performance relative to lower points in the plot. For comparison, the plot on the right side is DMTS 1-Second Delay condition means for the same subjects as the plot on the left. DMTS 10-Second Delay condition has a greater memory burden. Practice effect is nonsignificant and interaction is significant for the 10-Second Delay condition [$F_{(2,56)} = 0.31$, $p = 0.734$, $F_{(2,56)} = 3.69$, $p = 0.031$, respectively] and practice effect and interaction are nonsignificant for the 1-Second Delay condition [$F_{(2,56)} = 0.85$, $p = 0.433$, $F_{(2,56)} = 0.25$, $p = 0.776$, respectively].

score) response times did not show practice effect or reliable deficit across the three time points.

ANAM subtests M2S and CDD, on the other hand, showed a relatively greater error rate (>5%). For these 2 subtests, there was a pattern of mean differences in the Percent Correct variable suggesting an effect of exposure (Figs. 4 and 5). This pattern, however, did not meet the criterion for statistical significance in either M2S or CDD in this descriptive analysis.

DMTS is similar to the ANAM M2S subtest but is more difficult and consequently yields much greater error rates (33%) and much longer response times. Response times were mostly beyond 4 seconds, especially in the more difficult 10-second delay condition. Interpreting response times of this magnitude

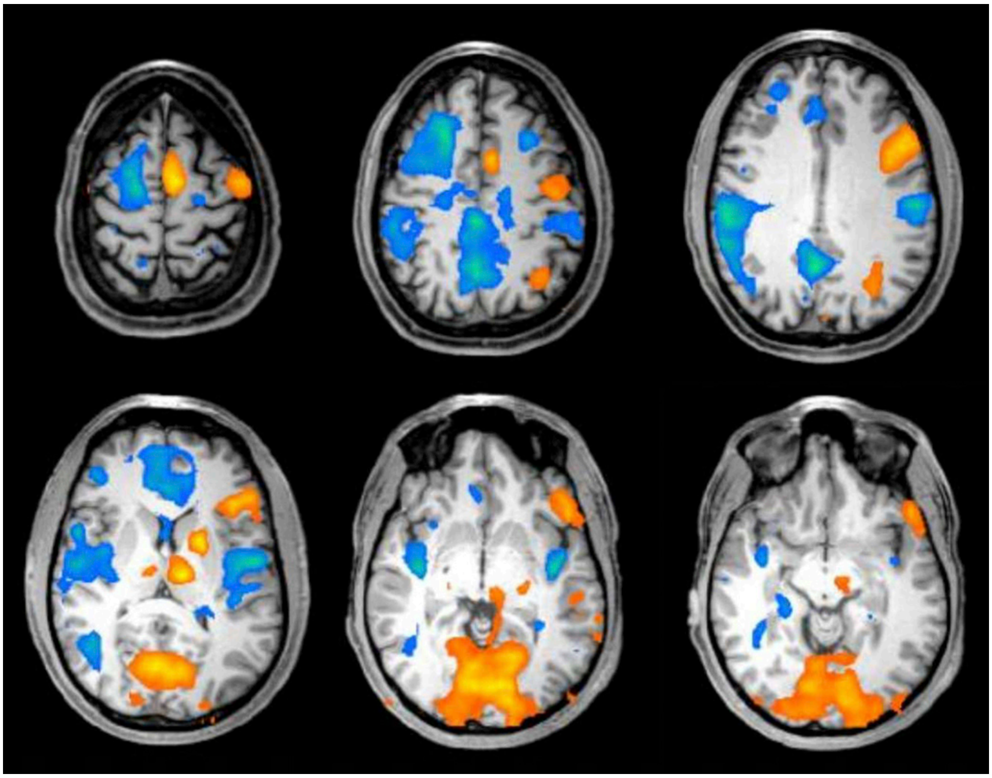

FIGURE 7. Pooled data acquired during the Sentence Completion Task. Clusters of increased activity are seen in the left frontoparietal and bilateral occipital regions. Decreased activity is seen along right lateral convexity, para-median frontal and parietal lobes, and within bilateral temporal lobes [random effects GLM: $t_{(54)} \geq 3.68$ or ≤ -3.68, $p \leq 5.25 \times 10^{-4}$].

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becomes unclear, as the task becomes more contemplative. In this consideration, Percent Correct is the DMTS variable presented in Figure 6. DMTS 10-second delay, as with ANAM M2S and CDD subtests, showed mean differences for the Instructor group in Percent Correct that were inconsistent with the more accurate responses of a practice effect. Like M2S and CDD, this pattern did not meet criterion for statistical significance when multiple comparisons are considered.

Neuroimaging

For n-back and sentence completion tasks, the general linear model (GLM) was calculated from BOLD sequences and compared to the expected hemodynamic response function for the stimulus paradigm. Analysis of covariance was performed to assess group differences. Activated clusters across all subjects during baseline and activation phases of the sentence completion task are shown in Figure 7 (random effects GLM: $t_{(54)} \geq 3.68$ or ≤ -3.68, $p \leq 5.25 \times 10^4$). Areas of activation are seen primarily within the left frontoparietal and bilateral occipital regions. Areas of decreased activation are seen along the right lateral convexity, the paramedian frontal and parietal lobes, and within bilateral temporal lobes. Activated clusters across all subjects for the n-back task are shown in Figure 8 (random effects GLM: $t_{(54)} \geq 3.65$ or ≤ -3.65, $p \leq 6.0 \times 10^{-4}$). Areas of activation are seen primarily within frontoparietal regions along the convexities with some activation in occipital lobes. In addition, areas of activation are seen with respect to the basal ganglia. Areas of decreased activation are seen within frontal, parietal, and occipital lobes near the interhemispheric fissure. Decreased activity is also seen within bilateral temporal lobes.

Repeated measures ANOVA comparisons were performed to determine whether cluster differences existed between Student and Instructor post-exposure examinations. No significant group differences were seen with the fMRI sentence completion task on either baseline to post-exposure comparisons by group or when comparing between groups. With the n-back task, comparison of baseline and post-exposure evaluations in Students demonstrated no significantly different activated clusters (random effects GLM: $t_{(37)} \geq 3.00$ or ≤ -3.00, $p \leq 0.005$). However, a single significantly different cluster was seen in the baseline to post-exposure Instructor comparison (random effects GLM: $t_{(7)} \geq 4.00$ or ≤ -4.00, $p \leq 0.005$). This cluster demonstrated increased activity in the post-exposure studies as compared to the baseline evaluations. As shown in frame A of Figure 9, this cluster localized to Brodmann area 47, which has been shown to be responsible for processing of syntax in spoken and signed languages. Also, comparison of Instructors to Students (random effects GLM: $t_{(22)} \geq 4.26$ or ≤ -4.26, $p \leq 3.5 \times 10^{-4}$) demonstrated increased activity within the Instructor group. The Instructor to Student group demonstrated four volumes of interest

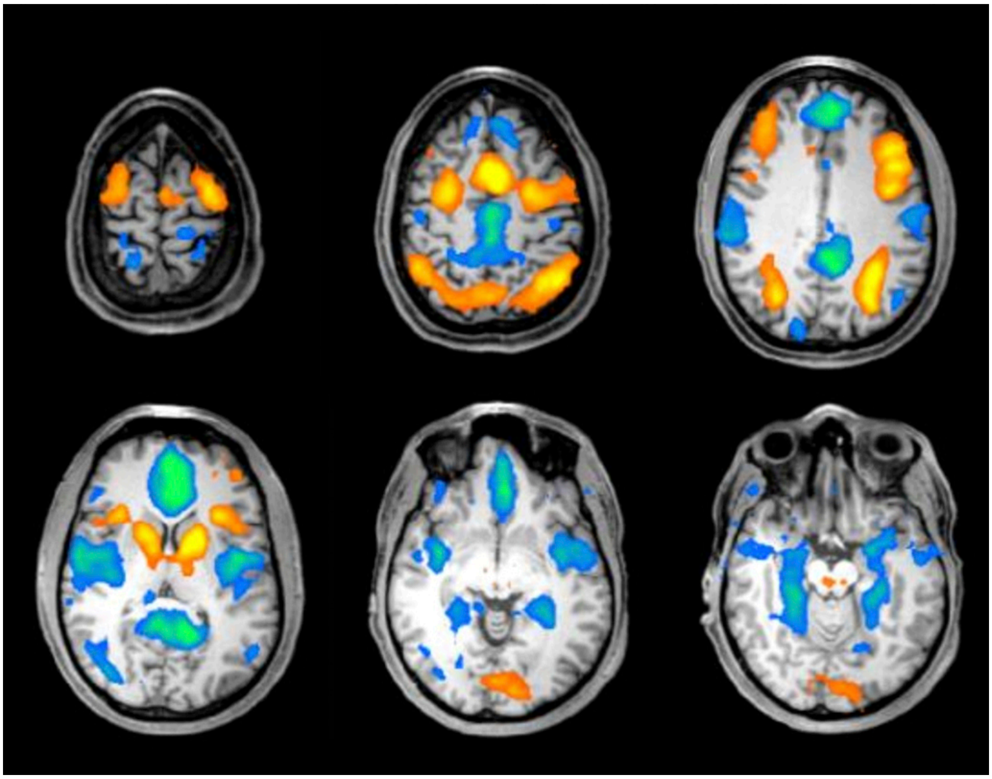

FIGURE 8. Pooled data acquired during n-back task. Clusters of activity are seen within frontoparietal, occipital and basal ganglia regions. Decreased activation is seen within frontal, parietal, occipital lobes near the interhemispheric fissure, and bilateral temporal lobes [random effects GLM: $t_{(54)} \geq 3.65$ or ≤ -3.65, $p \leq 6.0 \times 10^{-4}$].

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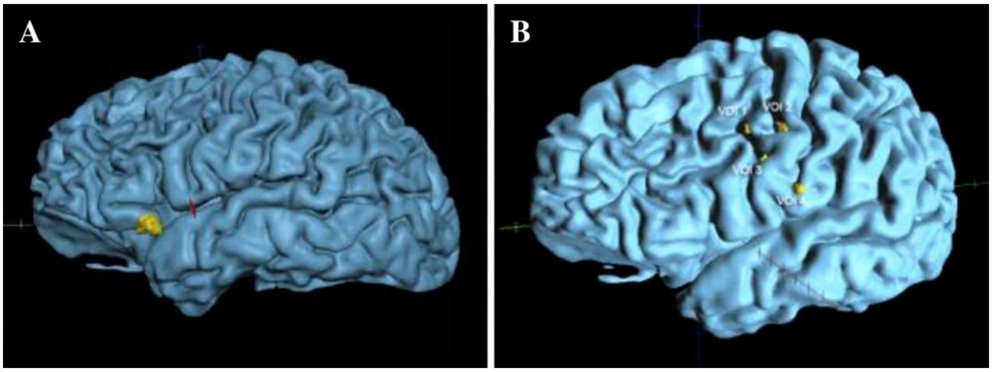

FIGURE 9. Volumetric reconstruction of axially acquired 3D T1-weighted sequences with blood-oxygen level-dependent imaging clusters shown to be significantly different in Instructor baseline vs. post-exposure (A) and in Instructor post-exposure vs. Student post-exposure (B) superimposed in yellow. Frame A demonstrates a single significantly different cluster in Brodmann area 47 [random effects GLM: $t_{(7)} \geq 4.00$ or ≤ -4.00, $p \leq 0.005$]. Frame B demonstrates 4 significantly different clusters, with 2 centered in Brodmann area 3, 1 in Brodmann area 7, and another in Brodmann area 40.

with increased activity. Two volumes of interest were located within Brodmann area 3 of the anterolateral postcentral gyrus, one within Brodmann area 7 of the anterior parietal cortex and the other in Brodmann area 40 of the anterior supramarginal gyrus (Fig. 9).

DISCUSSION

The measures employed before and after the 2-week breacher basic course and during the 6 days of exposure to repeated blast did not yield clear evidence for neurological impairment in breacher Students or Instructors. The results observed, however, did yield a description suggestive of blast-induced impairment in selected domains of cognition among individuals subject to sustained repetitive blast exposure. This description includes a reduction in accuracy of Instructor responses on tasks that place demand on memory ability, specifically, the 2 ANAM subtests M2S and CDD, the DMTS 10-second delay condition, and recognition for CVLT II auditory stimuli. Taken together, these results can be said to describe a pattern. It is the similarity across these tests that prompts our consideration. The fMRI BOLD signal increase during the n-back task for Instructors in their post-exposure studies and when compared with Students is consistent with the observations in behavioral data and with previous studies comparing fMRI n-back findings in mild TBI patients compared to matched controls.[11,12]

It is notable that evidence is seen in Instructors across measures that entail a memory demand and is not seen on measures that do not have a memory demand (i.e., CDS, PRO, and MTH; sentence completion for fMRI). A replication of the small effect, especially across modalities of neurocognitive and neuroimaging assessments, is consistent with concussion literature.[19]

While the current study constitutes the first report of n-back working memory task utilization in a population of human subjects exposed to repetitive low-level blast, previous studies employing the n-back task have demonstrated differing activation between mild TBI and control subjects.[13] Specifically, in a prospective evaluation of subjects that included a group presenting to an emergency room with symptoms consistent with mild TBI,[20] increased activation was seen within the right dorsolateral parietal and dorsolateral prefrontal cortex within patients with mild TBI as compared to controls. In addition, in a study of mild TBI subjects, 1 month after injury compared with healthy controls, moderate working memory load processing was associated with marked activity increases in bilateral frontal and parietal regions as compared to controls.[11] Further, in a separate study, differential patterns between mild TBI patients and matched controls demonstrated changes in brain activation persisting for up to 1 year following the initial insult.[12] Comparing these studies of mild TBI and the present study, fMRI observation of increased brain activation associated with exposure to environmental insult, it is hypothesized that this increased signal represents less-efficient metabolic function within the traumatically affected brain. While the findings of the current study are intriguing, they must be validated with a larger sample size in a longitudinal study.

The data collected in this study were sufficient for descriptive purposes. It may be that in future studies of the hypothesized relation between blast exposure and subclinical neurological insult in humans, an effective approach may depend on deep evaluation at the single subject level. The addition of breacher instrumentation in the current study provided critical data on subject load exposure, which has not been available in previous clinical and epidemiological work. When comparing the group neurocognitive and neuroimaging results in context of the recorded exposure data, the findings suggest that an individual's sensitivity to blast may be enhanced after multiple exposures. The period of time over which these exposures must occur for the sensitivity to manifest appears to be longer than the 2-week period of this study. This is supported by the fact that the findings in the neurocognitive tests and fMRI were among the Instructors, who, on average, had the lowest blast exposure levels over the 2-week period but who would have had a history of

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chronic blast exposure (at minimum, by virtue of prerequisites to become an Instructor and experience as an Instructor). The Instructors had more self-reported symptoms and greater mean difference changes in the targeted objective measures than the Student group. Based on the trends observed during this study, long-term chronic exposure to blast environments may increase the likelihood of developing neurological signs or symptoms consistent with concussion injury during subsequent blast re-exposure.

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