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TITLE: Diagnosing Contributions of Sensory and Cognitive Deficits to Hearing Dysfunction in Blast-Exposed/TBI Service Members

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14. ABSTRACT ***brief (~200 word) unclassified summary of most significant finding during the research period***

Blast-induced traumatic brain injury (TBI) and hearing loss are two of the most common injuries sustained as a result of the U.S. Global War on Terror. Recently, audiology clinics at DoD and VA healthcare centers have been reporting an increasing number of blast-exposed Service Members (SMs) complaining of having complications with speech comprehension in everyday social situations with competing talkers and interfering sounds despite having normal to near-normal audiometric thresholds. We hypothesized these speech comprehension problems might be the result of two possible mechanisms of injury: 1) damage to the auditory sensory periphery resulting in either cochlear dysfunction or the loss of auditory nerve fibers responsible for the encoding of suprathreshold sounds ("hidden hearing loss") or 2) blast-induced traumatic brain injury (TBI) to cortical networks associated with the processing of attention, working memory, speed of processing, and other executive functions related to speech and language processing. Results from a comprehensive battery of audiological, electrophysiological, and neuro-cognitive tests performed on blast-exposed SMs showed evidence of subclinical levels of sensory damage compared to SMs who had not been exposed to blast. These losses, however, are still within the range of what is typically considered "clinically" normal hearing. Different from what we observed in a earlier study of blast-exposed Veteran Administration (VA) SMs seeking treatment for post-traumatic stress disorder (PTSD) (Bressler, Goldberg, & Shinn-Cunningham, 2016), we found no evidence of cognitive deficits in attention or executive control in either the auditory or visual domains. However, neuro-cognitive outcomes for measures administered in the visual domain (thereby bypassing any peripheral auditory-system weakness) showed evidence that exposure to blast may have affected neural processing speed for language comprehension. Collectively, these findings suggest that problems associated with speech comprehension in complex acoustic environments in blast-exposed SMs with normal to near-normal pure-tone thresholds are likely due to a combination of bottom-up sensory processes as well as top-down neuro-cognitive processes. However, for the active-duty, blast-exposed military population, as opposed to a blast-exposed VA population, it appears that problems understanding speech in noise are primarily driven by subclinical deficits in hearing function (e.g., slight elevation in pure-tone thresholds, reduced distortion-product otoacoustic emissions) which result in degraded sensory input to already compromised networks responsible for cognitive processing of information.

15. SUBJECT TERMS

Subject recruitment, inclusion criteria change, control group data collection complete, blast-exposed group recruitment challenges, preliminary data analysis

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1. Introduction

Blast-exposed Service Members (SMs) returning from recent conflicts in Afghanistan and Iraq pose unique and challenging problems for the audiological community - many have normal to near-normal hearing thresholds, but have difficulty understanding speech, especially when the background includes competing speakers. From a clinical perspective, some of these SMs may have a Central Auditory Processing Disorder (CAPD) or cognitive deficits due to noise damage from one or more blast exposures. For some active-duty SMs, exposure to high-intensity blasts have been linked to cognitive dysfunction with or without a confirmed diagnosis of traumatic brain injury (TBI) or post traumatic stress disorder (PTSD). In addition to these two frequently occurring and co-occurring comorbidities, two additional independent factors may play a role in understanding what appears to be a functional hearing and communication deficit (FHCD) in spite of good audiometric thresholds. The first factor is related to supra-threshold auditory coding fidelity or peripheral distortion. The second factor is related to cortical control and attention, both of which can be adversely affected by exposure to blast. The goals of this study were to use objective electrophysiological tests (EEG) to quantify specific sensory and cognitive deficits contributing to FHCD, to determine how these are related to blast exposure, and ultimately to develop a clinically useful test battery of bottom-up and top-down tasks to quantify the role of each of these components on speech perception.

2. Keywords

Blast exposure, Central Auditory Processing Disorder (CAPD), functional hearing and communication deficit (FHCD), traumatic brain injury (TBI), hearing loss, cochlear neuropathy, electroencephalography (EEG), frequency following response to speech (FFR), envelope following response to modulated tones (EFR), auditory brainstem response (ABR)

3. Accomplishments

What were the major goals of the project?

The major goals of this study were 1) to study the effects of sensory versus cognitive processes on speech understanding in noise through the use of behavioral auditory and visual tasks, objective electrophysiological (EEG) tests, and subjective questionnaires regarding understanding speech under different environmental background condition, 2) to quantify specific sensory and cognitive deficits contributing to FHCD, and 3) to determine how metrics extracted from these different tests are related to blast exposure. For the final year of the grant, the primary focus was to increase subject recruitment and participation numbers of the blast-exposed subjects. Although we have met our recruitment targets for the non-blast control group, we were still shy of our target for the blast-exposed group. By the conclusion of the study, we had consented 130 (88 male) potential study candidates recruited at the Walter Reed National Military Medical Center (WRNMMC), of which 93 (57 male) were eligible for full participation. Not all tests were completed by all subjects and, after artifact rejection and noise reduction efforts were applied to EEG recordings to speech and non-speech stimuli, data from 84 subjects (64 controls and 20 blast-exposed) were analyzed.

What was accomplished under these goals?

SOW Major Task 4b: Complete data collection of control and blast group

In total, 84 participants (64 controls, 20 blast exposed) completed the subjective (SSQ), Behavioral (BTS) and Electrophysiological Test Sessions (ETS), yielding between 73–77 usable datasets per BTS task and 72–73 usable datasets per ETS task (see SOW Task 5a

below). The total number of usable data sets per task varied due to task-specific data rejection criteria (e.g., excessive noise in ETS data).

SOW Major Task 4: Participant recruitment and evaluations

Amendment to Y4 Annual Report:

The numbers we provided in last year's Y4 Annual Technical Report accidentally reflected the total number of subjects from two additional research sites, which are peripherally associated with this current project, but should not have been included in the subject counts. The numbers presented below are an accurate representation of subject participation at WRNMMC at the conclusion of the study. Recruitment during this last year benefited from our partnership with the Center for Neuroscience and Regenerative Medicine (CNRM). Through this partnership, we were able to enroll several new study candidates from this pool of potential subjects at a rate faster than we have been able to obtain in the past.

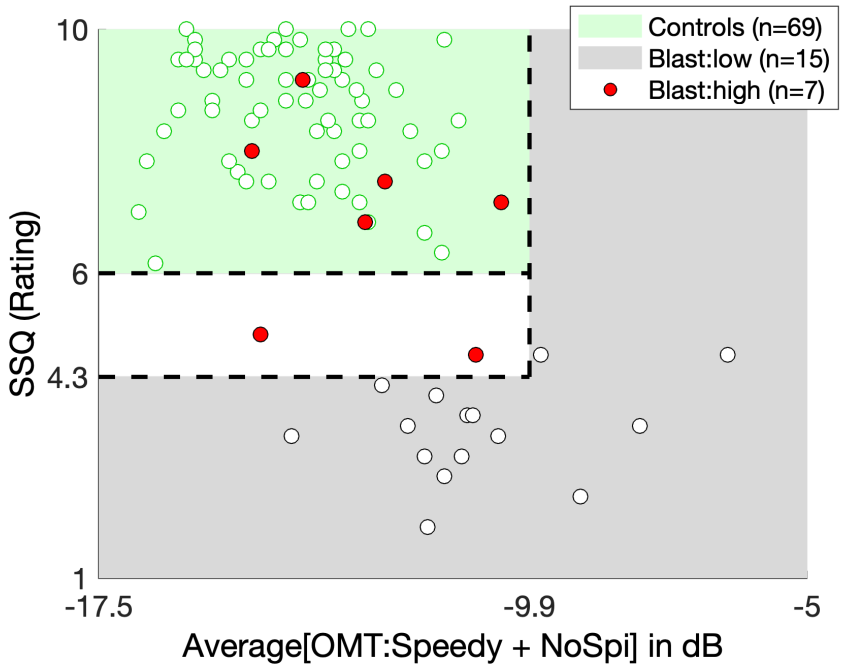


Figure 1: Subject group assignment based on two-factor inclusion criteria: the average of a 6-question SSQ survey (y-axis) and the combined detection thresholds in dB of a modified version (time compression and reverberation) of the Oldenburg Matrix speech-in-noise Test ($OMT_{TC\text{-}rev}$) and the N_0S_π detection threshold of a standard masking level difference test. The shaded green area delineates cutoff values for inclusion into the control group. The shaded gray area delineates inclusion criteria for blast:low subjects. Blast:high subjects (red) perform similarly to control subjects (falling within the green shaded region) on tests of speech recognition in noise and binaural processing.

- Total number of subjects consented = 130 (88 male, 42 female)
- Total number of eligible subjects = 93
    - Controls = 70 (34 male, 36 female)
    - Blast-Exposed = 14 male

- Blast-Exposed (BU only) = 9 male
- Study withdrawals = 9
  - Controls = 6 (3 male, 3 female)
  - Blast-Exposed = 3 male

SOW Major Task 5: Analyze and Disseminate Data

5a: Monitor data collection rates and data quality: summarized below

Number of subjects who completed the Electrophysiological Test Session (ETS) = 84

- Controls = 64 (31 male, 33 female)
- Blast-Exposed = 20 male

Breakdown summary of the completed datasets from the Electrophysiological Test Session (ETS) specific to W81XWH-15-1-0490:

- Auditory Selective Attention (ASA) = 81 (61 controls, 20 blast-exposed)
  - Usable data = 73 (55 controls, 18 blast-exposed)
- Visual Selective Attention (VSA) = 82 (63 controls, 19 blast-exposed)
  - Usable data = 72 (54 controls, 18 blast-exposed)
- Envelope-Following Response (EFR) = 86 (65 controls, 21 blast-exposed)
  - Usable data (56 controls, 20 blast-exposed)

For electrophysiological data, it is not unusual to exclude datasets due to the presence of excessive noise artifacts during the recording session. The "Usable data" category summarizes the number of quality datasets used in the analysis of the individual electrophysiological tests.

5b: Analyze research data

Research audiologists Dr. Kimberly Jenkins and Dr. Rebecca Lewis, research communications scientist Dr. Jennifer Myers, and research engineer Scott Bressler continued work on integrating the numerous datasets produced from the behavioral, electrophysiological, and neurocognitive test sessions. With the departure of Dr. Jenkins, this collaboration continued with a new research audiologist, Dr. Rebecca Lewis. Along with Co-PIs Drs. Barbara Shinn-Cunningham and Ken Grant, the team is in constant discussions as to how best to analyze and interpret the study findings.

5d: Work with data core and dissemination of findings. The research funded under award #W81XWH-15-1-0490 was combined with data from a previously funded multisite study (CDMRP Log#:DM170584 that tested a variety of auditory sensory and auditory and visual cognitive functions in the same study population. The primary measures added to the previous study were auditory and visual selective attention tasks (behavioral and EEG) and an envelope-modulation following response (EFR) at different depths of modulation.

Research Audiologist Dr. Kimberly Jenkins presented a poster at the 46th Annual Scientific and Technology Meeting of the American Audiological Society (AAS) in Scottsdale, AZ, entitled "Electrophysiological Responses in Blast and Non-Blast Exposed Military Service Members." Poster authors: Kimberly A. Jenkins, AuD, Jennifer R. Myers, PhD, Alessandro Presacco, PhD, and Ken W. Grant, PhD. 28-Feb-2019 to 02-Mar-2019.

Research Engineer, Scott Bressler presented a poster during the Topics in Physiological and Psychoacoustics (2aPPb) session at the 177th Meeting of the Acoustical Society of America in Louisville, KY, entitled "Blast Exposure in the Military and Its Effects on Sensory and Cognitive Processing." Poster authors: Scott Bressler, Kimberly Jenkins, Jennifer Myers, Ken Grant, and Barbara Shinn-Cunningham. 14-May-2019.

Research Engineer, Dr. Scott Bressler successfully defended his Ph.D. dissertation at Boston University, September 19, 2019.

SOW Major Task 6: Oversight and administration of the project

Research Engineer Scott Bressler, and Research Audiologists Dr. Kimberly Jenkins were in frequent contact with each other regarding the progress of subject recruitment and data collection. This same level of oversight continues with Dr. Jenkin's replacementd Dr. Rebecca Lewis.

To this end, Mr. Bressler made two trips each year to WRNMMC to discuss data collection and analysis with Research Audiologists Dr. Kimberly Jenkins and Dr. Rebecca Lewis, and Research Communications Scientist Dr. Jennifer Myers. These trips also provided Mr. Bressler with valuable face time with the team at Walter Reed to discuss recent results and data analysis strategies.

Summary of Mr. Bressler's trips to WRNMMC during final year:

- 04-Jun-2019 to 06-Jun-2019
    - EEG data analysis and review
- 19-Aug-2019 to 23-Aug-2019
    - EEG data analysis and review

6b: Submit quarterly reports for CDMRP submission
All three quarterly technical reports for year 5 were submitted.

6f: Develop scripts for analyzing results
Dr. Bressler continued to develop new and refined existing MATLAB data analysis scripts for summarizing individual and group data. Group summarized data can now be generated and updated as subjects complete the required measures from the Electrophysiological Test Sessions (ETS).

SOW Major Task 2: Hiring and Training of Research Audiologist

2a: Advertise and interview for Research Audiologist
The last quarter of this project year saw the departure of Research Audiologist Dr. Kimberly Jenkins and the hiring of her replacement, Dr. Rebecca Lewis.

2b: Audiologist hired and trained
Research Engineer Dr. Scott Bressler and Dr. Lewis were in frequent contact both over phone and email, as well as in person during one of Dr. Bressler's trips.

What opportunities for training and professional development has the project provided?

The EEG setup at WRNMMC provided Drs. Jenkins, Lewis, and Myers opportunities to refine their EEG data collection techniques. Additionally, as Drs. Jenkins and Lewis became more experienced programmers of MATLAB, they were able to analyze data in parallel with Dr. Bressler. With the departures of Dr. Lewis and Dr. Myers, a new research scientist was hired with extensive experience programming and analyzing EEG data. Dr. Ian Phillips, as well as our consulting engineer, are continuing to analyze data.

Dr. Bressler received important exposure to translational research in a clinical setting. His interactions with Dr. Grant and his lab broadened his knowledge in auditory neuroscience, audiology, and psychoacoustics. Mr. Bressler has took it upon himself to learn linear and non-linear regression modeling techniques to help determine which of the multiple test measures might be significant predictors of problems with speech comprehension in noisy environments, ***Aim 3*** of this project (To develop a clinically useful test batter to diagnose and isolate sensory and cognitive deficits that can produce hearing dysfunction in Service Members with H1 profile).

How were the results disseminated to communities of interest?

Dr. Jenkins presented a poster at the 46th Annual Scientific and Technology Meeting of the American Audiological Society held in Scottsdale, AZ between 28-Feb-2019 and 02-Mar-2019.

> "Electrophysiological Responses in Blast and Non-Blast Exposed Military Service Members." Poster authors: Kimberly A. Jenkins, AuD, Jennifer R. Myers, PhD, Alessandro Presacco, PhD, and Ken W. Grant, PhD

Research Engineer Dr. Scott Bressler presented a poster during the Topics in Physiological and Psychoacoustics (2aPPb) session at the 177th Meeting of the Acoustical Society of America in Louisville, KY. 14-May-2019

> "Blast Exposure in the Military and Its Effects on Sensory and Cognitive Processing." Poster authors: Scott Bressler, Kimberly Jenkins, Jennifer Myers, Ken Grant, and Barbara Shinn-Cunningham

Research Engineer Dr. Scott Bressler presented a virtual talk in defense of his Ph.D. dissertation, September 2019.

> "Blast Exposure in the Military and its effects on sensory and cognitive auditory processing" Boston University.

What do you plan to do during the next reporting period to accomplish the goals?

As this report reflects the final report under this grant, there will be no next reporting period. However, the team is currently in the process of writing and submitting manuscripts from the work funded on this grant.

4. Impact

What was the impact on the development of the principal discipline(s) of the project?

Results suggest that even for subjects classified as having normal to near-normal hearing, exposure to one or more explosive blasts can negatively impact suprathreshold cochlear function as indicated by poorer audiometric thresholds (**Figure 2**), clinically present but weak

DPOAEs, (**Figure 3**), elevated ABR wave V:1 ratio (**Figure 4**), reduced internal signal to noise levels (**Figure 5, middle panel**), and reduced internal stability (**Figure 5, bottom panel**). This reduction in cochlear function in the blast-exposed subjects appears to be consistent with self-reported complications with hearing in everyday listening scenarios as measured by an abbreviated 6-question version of the Speech, Spatial, Qualities Questionnaire (Gatehouse and Noble, 2004; Grant et al., manuscript submitted to Ear and Hearing).

Tests of the auditory periphery (pure tone audiometric thresholds, DPOAEs, and to some extent the ABR and speech frequency following responses) showed consistent differences between control subjects with no history of blast exposure, blast-exposed subjects who present with lower levels of functional hearing performance (blast:low), and blast-exposed subjects who demonstrate levels of function hearing performance similar to those of the non-blast control subjects (blast:high).

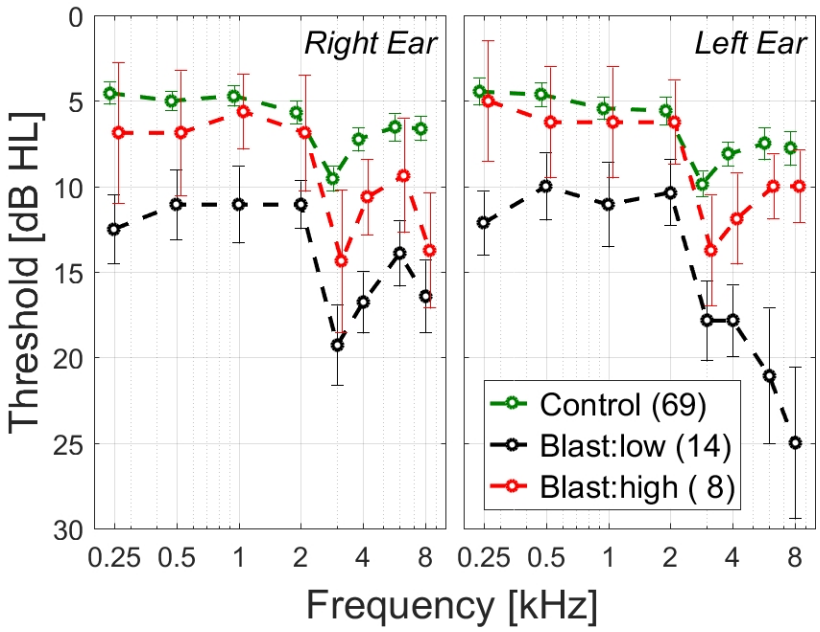


Figure 2: Pure tone air conduction thresholds comparing non-blast controls (green), blast-exposed subjects with good functional hearing performance (Blast:high, red), and blast-exposed subjects with poor functional hearing performance (Blast:low, black). Symbols and error bars represent means and ±1 standard deviation, respectively, for each subject group.

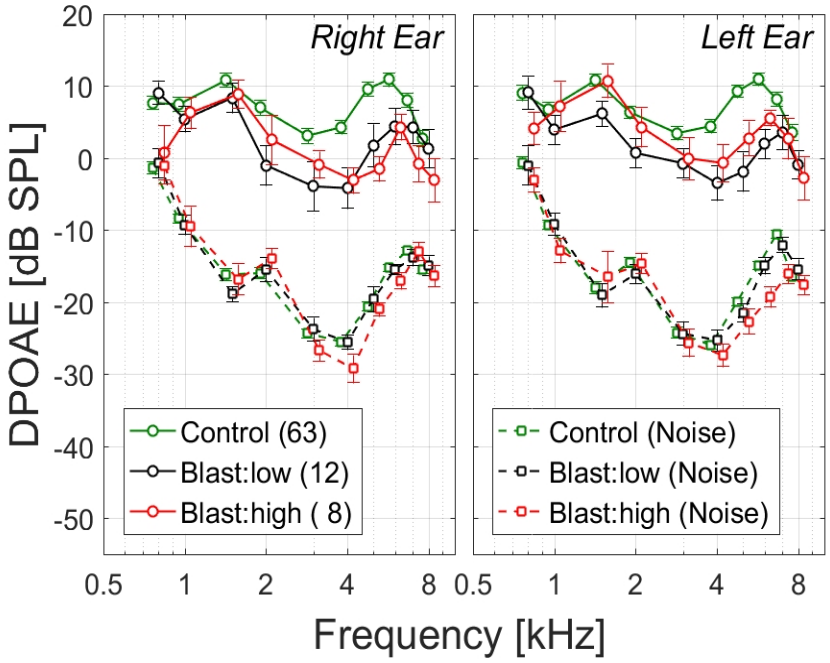


Figure 3: Distortion product otoacoustic emissions (DPOAEs) for Control (green), Blast:high (red), and Blast:low (black) subjects. Solid curves with round symbols depict DPOAE magnitudes and dashed curves with square symbols denote the corresponding noise floor in each case. Symbols and error bars represent means and ±1 standard deviation, respectively, for each subject group.

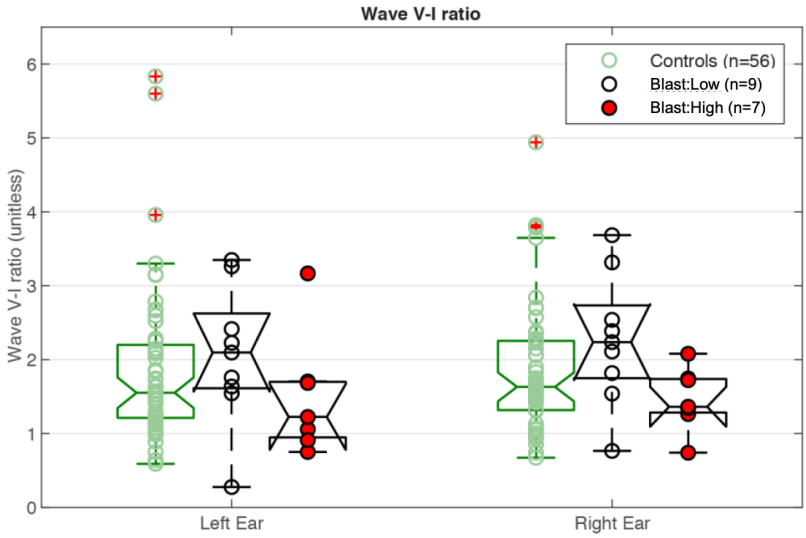


Figure 4: Auditory Brainstem Response Wave V-I ratio

Of the various stereotypical ABR waveform peaks, the amplitudes and latencies of Waves I, III, and V are thought to reflect the neural activity of the auditory nerve, superior olivary complex, and inferior colliculus. respectively. Figure 4 shows the ratio of Wave V to Wave I amplitudes for the three groups.

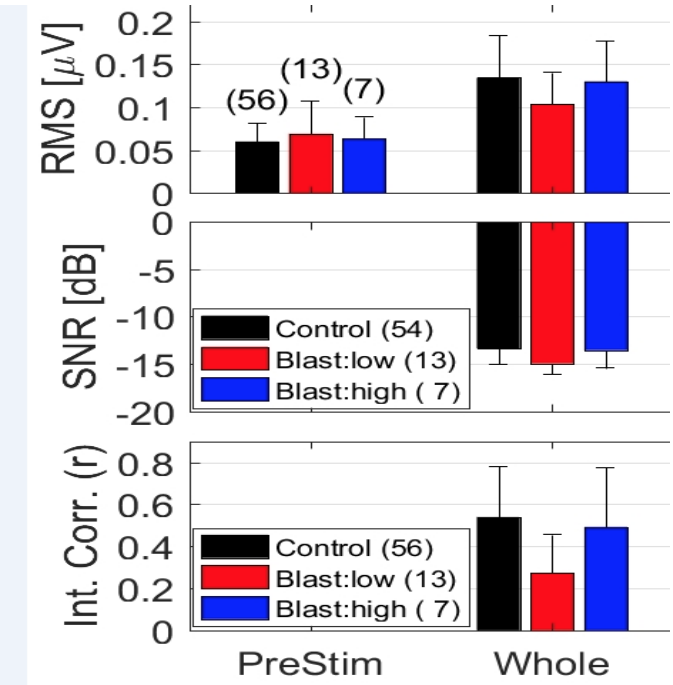


Figure 5. Auditory brainstem measures to 100-Hz consonant-vowel syllable /da/. Top Panel: Energy profiles for control subjects, blast:high subjects and blast:low subjects. Note that the blast:low subjects had a slightly smaller response to the speech stimulus fundamental frequency (whole) and a slightly larger response (background pre-stimulus EEG levels) when no stimulus was presented. Middle Panel: Internal signal-to-noise (SNR) levels for the three subject groups showing the poorest SNR for the blast:low subjects and similar performance for blast:high and control subjects. Bottom Panel: Internal stability metric. Note, the EEG response to the speech signal displayed greater stability (less variability) from sweep to sweep for the control and blast:high groups than for the blast:low group.

Figure 5 shows the complex ABR to a synthetic speech consonant-vowel syllable with a fixed fundamental frequency (F0) of 100 Hz. The responses to approximately 2000 sweeps of the syllable /da/ were averaged and the spectral magnitude of the component at the syllable F0 was extracted. In addition, the EEG measured in-between syllable presentations were averaged to obtain an estimate of the internal noise present when no stimulus is presented. These two values, the evoked response magnitude relative to the internal noise estimates in the absence of any signal, yield an internal signal-to-noise ratio. Finally, the stability of the evoked response was estimated by computing the Pearson-Product correlation between the average of 1000 sweeps (chosen randomly without replacement) to its complement (remaining 1000 sweeps). This process was repeated 100 times for each subject to obtain an estimate of the variability of the evoked response. As shown in Figure 5, the averaged evoked response for the control and Blast:high subjects was greater than the averaged evoked response for the Blast:Low group (top panel, right) while at the same time, the average response when no stimulus was presented (top panel, left side) was greater for the Blast:Low group than the control or Blast:High groups. The weaker evoked response coupled with a greater pre-stimulus internal response for Blast:Low subjects led to a poorer signal-to-noise ratio (SNR) than the other two groups (middle panel). This poor SNR was reflected in and quantified by the low stimulus evoked response stability for Blast:Low subjects compared to control or Blast:High subjects (bottom panel).

In addition to sensory deficits shown for blast:low performers, cognitive factors, such as attention, working memory, and speed of processing, an auditory and visual task adapted from Bressler et al (2016) was run. Unlike earlier results from VA subjects (Bressler, et al., 2016), the Auditory (ASA) and Visual Selective Attention (VSA) behavioral and EEG measures showed no significant differences in the current study between control and blast-exposed groups. Findings from these analyses are being processed and finalized and a manuscript is in preparation. These data are also included as a chapter in Dr. Bressler's doctoral dissertation.

Figures 6 shows the results for the auditory selective attention task (ASA). This task had subjects listen to three co-occurring melodies spatially located to the left, in front of, and to the right of the subject's head. On each trial, a cue tone spatially located to the left or right and having a pitch centered within the frequency range of the target melody pitch contour was presented to alert the subject as to which melody to attend. The subject then identified the target melody as having a pitch contour that was rising, falling , or changed direction. EEG responses, triggered by the start of each tone in the target and non-target melodies, were also recorded. Behaviorally, all three subject groups showed little or no difficulty tracking and attending to the target melody and correctly identifying the melody contour. The boxplots in the left-hand panel of Figure 6 show the median, quartile distribution,, ± 95% confidence limits (indicated by the notches in the box plot), and outliers (red crosses) for performance (proportion of trials) for the control and two blast-exposed groups . As seen in Figure 6 (left panel), when the attended tone was lagging or leading, identification scores were roughly 90% correct. Data shown in the right-hand panel of Figure 6 shows the subject's ability to inhibit a response when so instructed. As can be seen, the false alarm rate was very low for all groups.

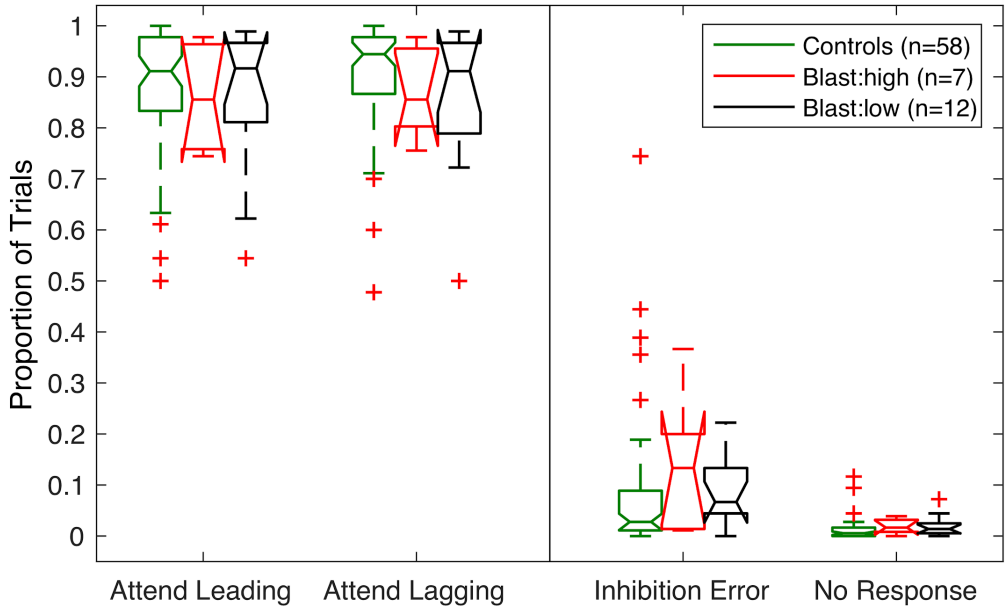


Figure 6: Behavioral results for the Auditory Selective Attention (ASA) task. Left panel: percent correct identification of attended signals. Right panel: executive control as indicated by subjects' ability to suppress their response when so instructed.

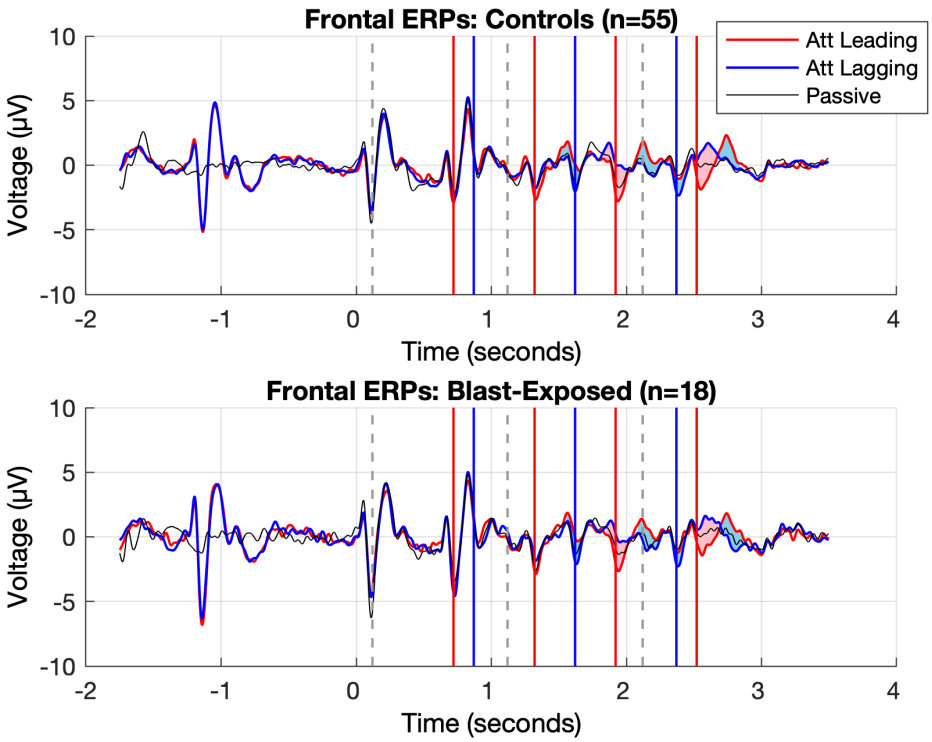


Figure 7: Auditory evoked responses from the average of five frontal EEG channels for controls (top) and blast-exposed (bottom) subjects. Gray shaded areas highlight statistically significant differences between attend leading (red) and attend lagging (blue) conditions.

Figure 7 shows the across-subject average auditory evoked response potentials (averaged across frontal-central electrodes AF3, AF4, F3, F4, and Fz) to identical three-melody stimuli under the three different attentional conditions: attend to the leading melody (red), attend to the lagging melody (blue), and the passive listening case (black). The top panel shows results for control subjects while the bottom panel shows results for blast subjects (combining low- and high-performing groups). The shaded regions in both subplots highlight the contrast between the attend leading and attend lagging conditions. Consistent with what we have observed previously (Bressler et al., 2016; Choi et al., 2014), both groups show enhanced N1 peak responses to the onsets of the individual notes of a melody when it is attended compared to when that melody is ignored. Pink-shaded regions show when the N1 response peaks in the attend leading conditions are stronger (more negative) compared to the attend lagging/ignore leading condition. These regions coincide with predicted N1 peak latencies, approximately 120 milliseconds after note onset (highlighted by the red vertical lines). Similarly, the light blue-shaded regions show enhanced N1 responses to the last two note onsets of the attended lagging melody (see blue vertical lines for reference). Because the cluster-level analysis was performed on the entire trial period, there are also regions that highlight differences between the later P2 peaks (positive peak deflections 200 millisecond post note onset) in the attending leading case (red line plot); this is largely the results of the temporal spacing of the note onsets in leading melody and their position relative to the notes in the competing lagging melody. Statistical comparisons across all three attentional conditions using a non-parametric cluster-level analysis method (Maris & Oostenveld, 2007) showed no differences at any time point within the trial epoch between the blast and non-blast controls. The test statistic we used was based on the sum of clustered time-adjacent samples

with t-values (two-sample t-test, df = 62) exceeding a user-selected 95th quantile threshold of a two-tailed t-distribution. The null distribution and corresponding 5% alpha significance level of this test statistic was derived through 1000 group-level permutations.

Analogous to the auditory selective attention task, a visual selective attention (VSA) task was devised, shown schematically in Figure 8. In this task, tones making up the three melodies in the ASA task were replaced by arrows in a visual field of attended and unattended arrows. The VSA task was essentially the same as in the ASA task, namely to identify the contour of sequentially presented visual arrows as up-going, down-going, or a change in direction (zig-zag).

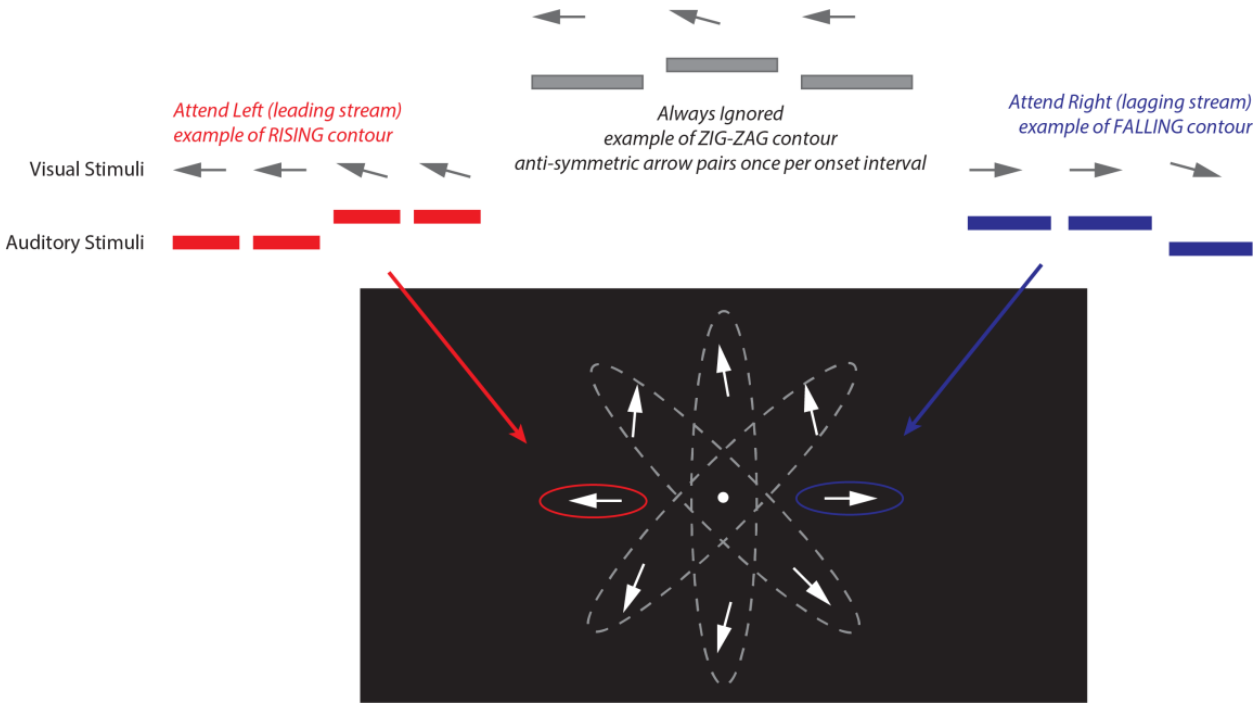


Figure 8: Visual Selective Attention task. Graphical representation of the analogous "rising, falling, and zig-zagging" melodic contours from the Auditory Selective Attention task are provided for reference.

Behavioral data for the VSA task are shown in Figure 9. As with the ASA task, subjects showed little or no difficulty correctly identifying the contour of the target stimulus (left panel), or withholding their response when so instructed (right panel).

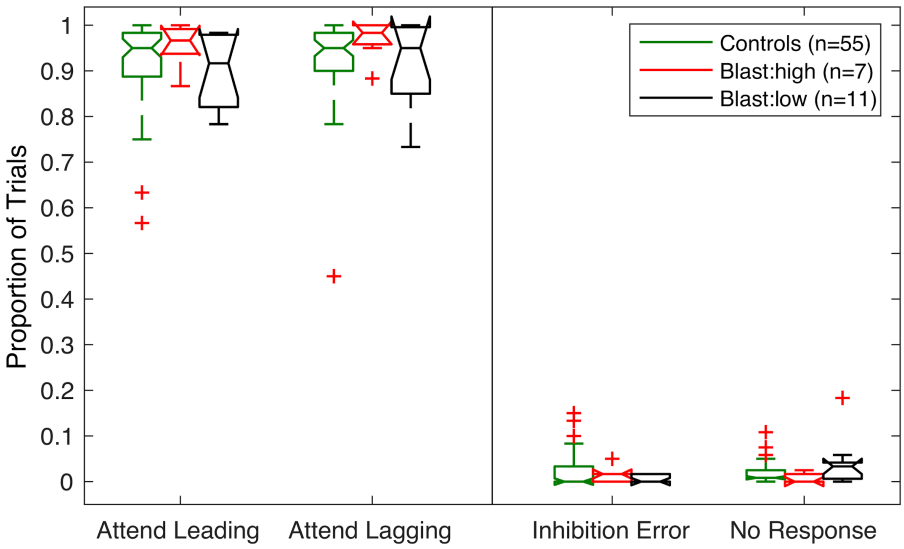


Figure 9: Behavioral results for the Visual Selective Attention (ASA) task. Left panel: percent correct identification of attended signals. Right panel: executive control as indicated by subjects' ability to suppress their response when so instructed.

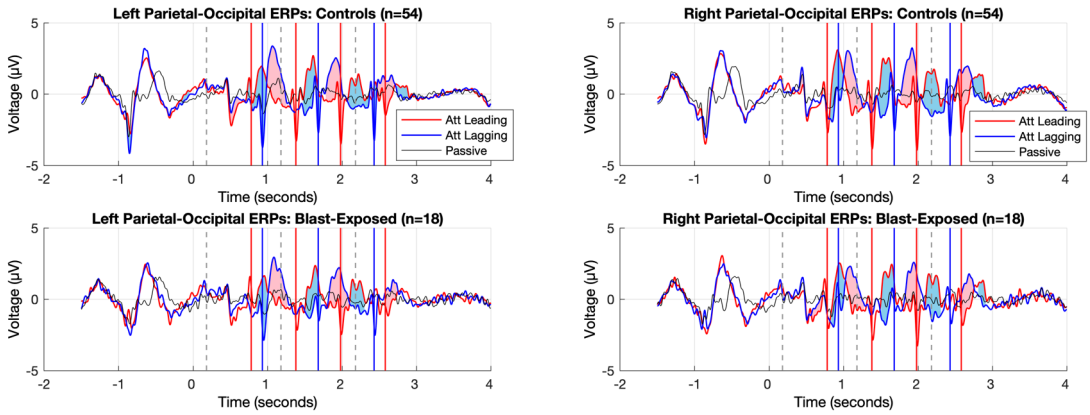


Figure 10: Visual evoked responses from left and right hemispheric parietal-occipital electrodes.

Figure 10 shows the averaged EEG responses from the left and right parietal-occipital electrodes for control subjects (top) and blast subjects (bottom). Areas shaded in gray represent statistically significant differences ($p<0.05$) between attend leading and attend lagging conditions. As with the ASA task, the VSA task showed no differences between subject groups.

Neurocognitive Test Battery. In addition to the ASA and VSA objective EEG measures, a set of standardized cognitive tests was also administered to subjects. In some cases, cognitive tests were administered in the auditory modality while for other tests, stimuli were presented in the visual modality. These tests were used to compare cognitive behavioral and objective tests and to help rule out a weakened periphery for blast-exposed subjects. The neurocognitive test battery consisted of tests of attention, processing speed, working memory and memory.

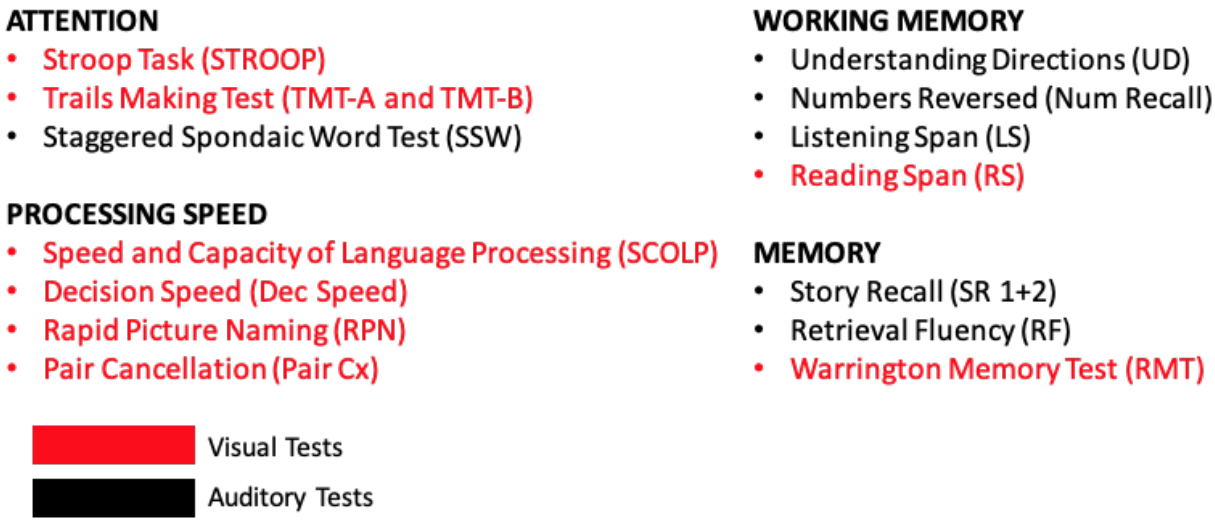


Figure 11. NeuroCognitive Test Battery. For each test, the bottom 5th percentile cutoff score for the control group was used to determine a failure rate for the two blast-exposed groups. The expected failure rate for the control subjects was 5%. Red=Visual Test, Black=Auditory Test. For the Understanding Directions test, directions were given auditorily (e.g., "show me the trapeze artist with arms outstretched, but not one wearing blue or pink") while the subjects' response involved interpretation of a visual scene. Some tests cut across domains listed. For example, RMT is a test of memory but also processing speed since it can be scored as the number of words correctly identified as meaningful versus nonsense in a fixed amount of time.

Results from the neurocognitive assessments, expressed in terms of the failure rates for control and Blast:Low subjects, are shown in Figure 12. Failure rates were based on the 5th percentile cutoff values for each test for control subjects. The expected failure rate for control subjects was 5% (white bars). Note that failure rates for the Blast:High group are not shown. Recall that Blast:High subjects had sensory performance scores (speech in noise, binaural processing) and subjective levels of perceived difficulty understanding speech (SSQ questionnaire) that fell within the distribution of screening scores of control subjects. As a result, the decision was made not to run these few subjects on the neurocognitive assessment battery.

Failure rates for the control group were around 5% as expected. Failure rates for the Blast:Low group (gray bars) were higher than that for controls for most of the tests. Failure rates greater than 20% suggest a substantial departure from the nominal 5% rate for controls. These include Rapid Picture Naming, SCOLP (semantic and sentences), and Listening Span. Of these four tests, three were administered in the visual domain and all but the Listening Span (auditory test of working memory) were tests of processing speed. Tests that showed a moderate difference between Blast:low and control subjects (10-19% failure rates) were the Warrington Recognition Memory Test, Retrieval Fluency, Trail Making Test A, STROOP, and Decision Speed. Of these five tests, four were administered in the visual domain, two were tests of attention and cognitive flexibility (i.e., Stroop and Trail Making Test), and three were predominantly tests of processing speed (Decision Specd, SCOLP, and RMT) .

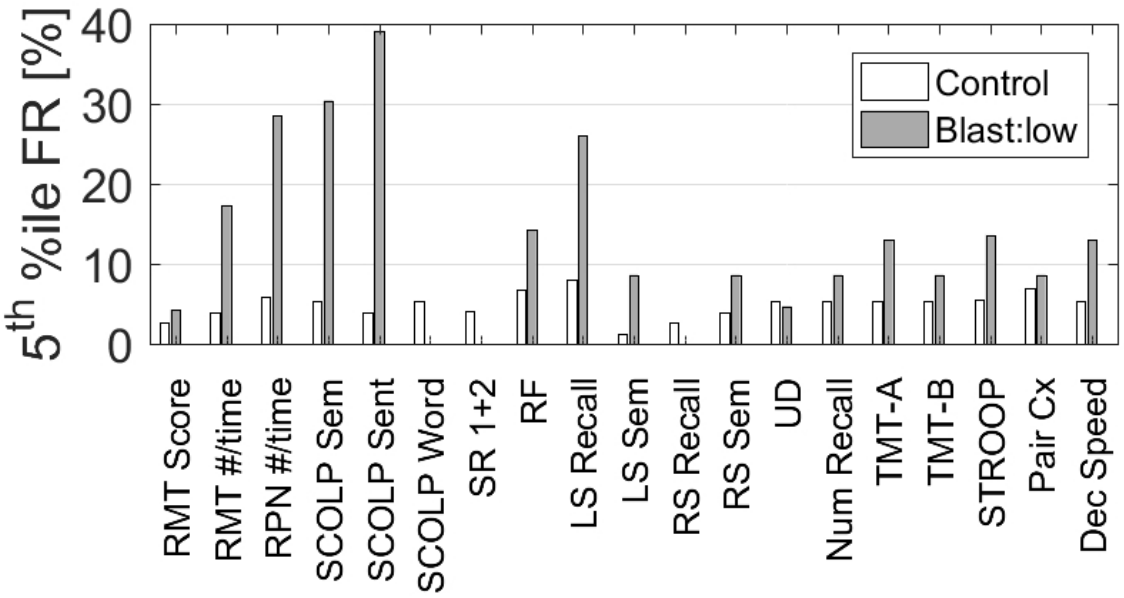


Figure 12. Failure rates (number of subjects falling in the bottom 5th percentile of the control subjects) for each test in the neurocognitive assessment battery. Control subjects (white bars), Blast:Low subjects (gray bars), Blast:High subjects (black bars). Failure rates for the Blast:High group were zero, owing in part to the small number of subjects in this group.

Discussion

Results Summary: This study sought to understand why some SMs, especially those exposed to explosive blasts, report problems understanding speech in noise and other everyday environments even though their audiometric thresholds are within the normal range. Two basic hypotheses were considered:

1) Exposure to blast has caused damage to the auditory sensory periphery resulting in a degraded neural representation of the spectro-temporal acoustic information necessary to understand speech in noise.
2) Blast exposure has caused damage to local cortical networks and/or the long-range axonal connections between networks involved in the processing of attention and working memory.

To address these issues, a test battery that included behavioral, electrophysiological, and subjective measures of sensory and cognitive speech communication abilities was used with speech and non-speech signals presented to both auditory and visual modalities. The primary questions were whether military exposures to noise, weapons fire, and explosive blasts had measurable effects on functional hearing and communication even though hearing thresholds were normal or near normal. The residual after-effects of blast exposures on sensory and cognitive function have been suggested before, but those studies were not fully able to address whether observed deficits in attention, executive function, working memory, or speed of language processing could be separated from a weakened auditory periphery. By incorporating subsets of sensory, central auditory processing, as well as cognitive tests presented to the visual modality, we were able to essentially bypass the impaired auditory periphery and auditory brainstem processes to assess more general cognitive communication deficits. As a result, we can

state that exposure to explosive blasts when close enough to feel the heat and/or pressure wave can result in a combination of sensory damage (hidden hearing loss) and cognitive damage, especially as it pertains to the speed of comprehension and language processing.

What was the impact on other disciplines?

Our data suggest that current audiological standards for classifying "normal hearing" may be too general and can fail to identify individuals "at risk" for speech communication deficits. It appears that pure tone thresholds of 15-20 dB HL, while still technically normal, may in fact be affecting a person's ability to communicate in complex listening environments. If confirmed, this may lead to changes in the way sub-clinical hearing loss is categorized and treated at the Walter Reed Audiology and Speech Pathology Clinic. American Speech-Language-Hearing Association (ASHA) guidelines define normal hearing as hearing thresholds between -10 to +15 dB HL. While the American Academy of Audiology (AAA) guidelines define normal hearing to be between -10 to 20 dB HL. Our data show clear evidence of abnormal peripheral auditory processing for signals that are fully audible.

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. Changes/Problems

Changes in approach and reason for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

- As of the writing of this report, research engineer Scott Bressler, has successfully defended his doctoral thesis and taken a position at a start-up company. The PI, Dr. Shinn-Cunningham, has taken a new appointment at Carnegie Mellon with considerable administrative responsibilities . Drs. Rebecca Lewis and Jennifer Myers have also taken new positions within the private sector. In response to these changes in effort on the project , we have hired a research associate with experience in EEG testing and analyses, which will ensure project data, analysis scripts, and other relevant documents are properly transitioned over to the care of Co-PI Dr. Ken Grant and research associate Dr. Ian Phillips. Dr . Bressler continues to assist the project as a contracted hire.
- We have applied for and received a second one-year no-cost extension, which allowed for a modest increase in the numbers in the experimental blast groups. However, with COVID-19 restrictions in place at Walter Reed, only a handful of subjects were recruited.
- Despite being in two different locations, Dr . Bressler and Dr. Shinn-Cunningham have been in close communication and continue to review and monitor the latest results and overall progress of the project.

Limitations of the Study:

- Changing War Posture. Since 2013 there has been a drawdown of the war efforts in Iraq and Afghanistan, leading to fewer SMs returning with injuries due to blast exposure. Although the study duration was increased through two no-cost extensions, recruitment of blast:low or blast:high subjects became challenging. In March 2020, COVID restrictions initially closed the research labs and weren't opened fully until October 2020. At that time, recruitment resumed but at a very slow pace because of subjects' reluctance to come to Walter Reed during the pandemic.

- Age: The criteria for subject recruitment was for individuals to be between the ages of 18-55. It was expected that blast exposures would increase with years of service, making the average age of the blast:low and blast:high subjects greater than the mean age of the control group. Analyses are underway to match age across groups by eliminating the younger members of the control group. Even so, average age differences between blast and non-blast groups remained. This persistent age difference across blast versus non-blast groups can affect cognitive measures; therefore, norm-adjusted values are being considered.
- Gender: Although women and men were represented fairly equally in the control group, very few women reported being exposed to combat blast explosions. In addition, the women in the control group tended to be younger than the men. Thus, when subjects were matched in age, essentially all of the (younger) women in the control group were eliminated. With the under-representation of women in the blast groups, it will not be possible to rule out gender as a factor (e.g., women both tend to have better hearing thresholds and are exposed to less hazardous noise).

Future Directions Low-gain hearing aid (LGHA). Many SMs with a history of noise-/blast-exposure with or without concomitant mild traumatic brain injury (mTBI) receive audiometric evaluations. Clinically, additional measures are often collected in an attempt to quantify auditory processing abilities due to SMs self-reported difficulties comprehending speech-in-noise with resulting negative functional limitations on their activities of daily living. For many, standard audiometric measures (i.e., audiogram, tympanometry, words in quiet) do not capture subjective complaints, especially when the audiogram is within normal limits. Based on currently available evaluation methods, these SMs may then be diagnosed with either peripheral hearing loss or acquired CAPD in the absence of peripheral hearing loss. A variety of test batteries, diagnostic inclusion criteria, and remediation techniques to limit the negative impacts of acquired APD currently exist, with many of these individuals ultimately being fit with LGHAs despite the lack of objective evidence to support efficacy and validity of such treatment (Saunders et al.2015, Gallun et al. 2012a; Gallun et al 2012b). Further, our understanding of the potential role of peripheral dysfunction in LGHA treatment outcomes for acquired APD (i.e., due to mTBI and blast/noise exposure) in the presence of NHT is minimal, thus necessitating the need to investigate the relationship between peripheral status and outcomes obtained from LGHAs in these patients. We currently do not understand why such small amounts of amplification (often only 5 dB) result in patient satisfaction or objective benefits when no audibility problem can be demonstrated. The data observed in the present study seems to suggest that even this small amount of HA gain would improve the ***internal*** SNR (evoked response to speech relative to the internal noise levels recorded in the absence of a stimulus). A ny amount of gain that could be applied to the stimulus without simultaneously increasing background noise levels would thus improve the internal representation of auditory information. While HAs have a very difficult time achieving SNR advantages in real-world complex environments, HA usage in quiet might be giving the auditory processing system just enough boost to overcome some of the elevated neural background noise.

Auditory and/or Cognitive training. Outside the DoD or the VA where advanced HAs are provided for free or at cost, within the civilian world, the cost of modern HAs in the absence of elevated hearing thresholds may be prohibitive. In these cases, or for those that have tried HAs with little success, or even those with successful use of HA technology, training the

brain to process speech faster or to decode distorted speech from a weakened and damaged sensory periphery should help, regardless of whether HAs are being used. The crucial issue with auditory or cognitive training is one of compliance with the training protocols. Cognitive training has a long and checkered history with little benefits overall being shown. However, the vast majority of studies reporting on the efficacy of cognitive or auditory training on speech understanding in noise reported serious compliance issues where patients might start "training" only to quit after a few sessions.The effects of auditory and cognitive training on speech understanding, or the effects of HAs in combination with auditory and cognitive training, are mostly unknown.

Changes that had a significant impact on expenditures

Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report

Significant changes in use or care of human subjects

Nothing to report

Significant changes in use or care of vertebrate animals

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. Products

Publications, conference papers, and presentations

Journal publications

Two to three planned manuscripts are currently being discussed

Books or other non-periodical, one-time publications

Nothing to report

Other publications, conference papers, and presentations

Conference posters:

Kimberly A. Jenkins, AuD, Jennifer R. Myers, PhD, Alessandro Presacco, PhD, and Ken W. Grant, PhD, "Electrophysiological Responses in Blast and Non-Blast Exposed Military Service Members." 46th Annual Scientific and Technology Meeting of the American Audiological Society held in Scottsdale, AZ between 28-Feb-2019 and 02-Mar-2019.

Scott Bressler, Kimberly Jenkins, Jennifer Myers, Ken Grant, and Barbara Shinn-Cunningham, "Blast Exposure in the Military and Its Effects on Sensory and Cognitive Processing." 177th Meeting of the Acoustical Society of America in Louisville, KY. 14-May-2019

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

Nothing to report

Inventions, patent applications, and/or licenses

Nothing to report

Other products

Nothing to report

7. Participants and Other Collaborating Organizations

What individuals have worked on the project?

Name:	Prof. Barbara Shinn-Cunningham
Project Role:	Principal Investigator
Research Identifier:	0000-0002-5096-5914
Nearest person month worked:	2.4
Contribution to project:	
Funding support:	

Name:	Dr. Kenneth Grant
Project Role:	Co-Principal Investigator
Research Identifier:	
Nearest person month worked:	1.2
Contribution to project:	
Funding support:	

Name:	Scott Bressler
Project Role:	Research Engineer/Graduate Student
Research Identifier:	
Nearest person month worked:	12
Contribution to project:	Dr. Bressler was responsible for the procurement and installation of the research hardware, development of the experimental and data analysis software, and training Research Audiologists, Drs. Jenkins and Lewis, and Research Communications Scientist, Dr. Myers, in EEG data collection and analysis techniques. He was also instrumental in filing the quarterly technical progress reports.
Funding support:	

Name:	Dr. Kimberly Jenkins
Project Role:	Research Audiologist
Research Identifier:	
Nearest person month worked:	9 (hired 17-Jan-2017)
Contribution to project:	Dr. Jenkins was responsible for subject scheduling, evaluation, data collection, and data archiving. She represents the main point of contact for the study participants and was Mr. Bressler's direct contact for all technical and/or equipment related issues up until the time when Dr. Lewis replaced her.

Funding support:	

Name:	Dr. Jennifer Myers
Project Role:	Research Communications Scientist
Research Identifier:	
Nearest person month worked:	12 (hired 14-Nov-2016)
Contribution to project:	Dr. Myers was responsible for Phases I & II of the CAPD Prevalence Study to which the BU study is attached. Along with Dr. Jenkins, she was also a main point of contact for the study participants, and a secondary contact for Dr. Bressler on EEG-related hardware, software, and data collection issues.
Funding support:	CAPD Prevalence Study

Name:	Dr. Rebecca Lewis
Project Role:	Research Audiologist
Research Identifier:	
Nearest person month worked:	1
Contribution to project:	Dr. Lewis was the new project research audiologist, a position recently vacated by Dr. Jenkins in June of 2019. Dr. Lewis was hired in August 2019 and left the project one year later.
Funding support:	CAPD Prevalence Study

Name:	Tom Heil
Project Role:	Engineer
Research Identifier:	
Nearest person month worked:	0.6
Contribution to project:	Mr. Heil has provided valuable technical support of the EEG hardware and software infrastructure.
Funding support:	CAPD Prevalence Study

Has there been a change in the active or support of the PD/PI(s) or senior key personnel since the last reporting period?

Nothing to report

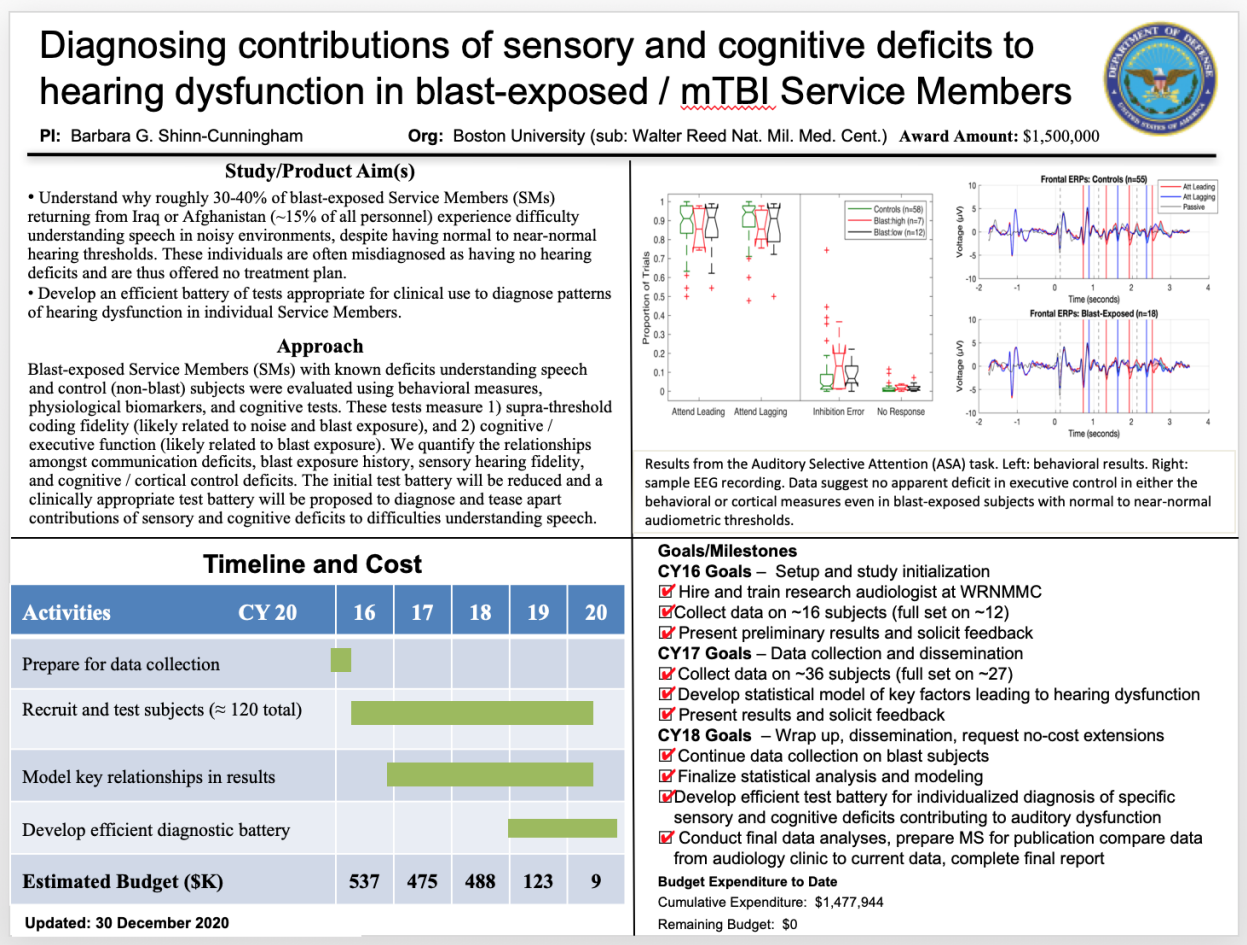
What other organizations were involved as partners?

Nothing to report

8. Special Reporting Requirements

Collaborative awards

Quad charts



9. Appendices

Conference Presentations

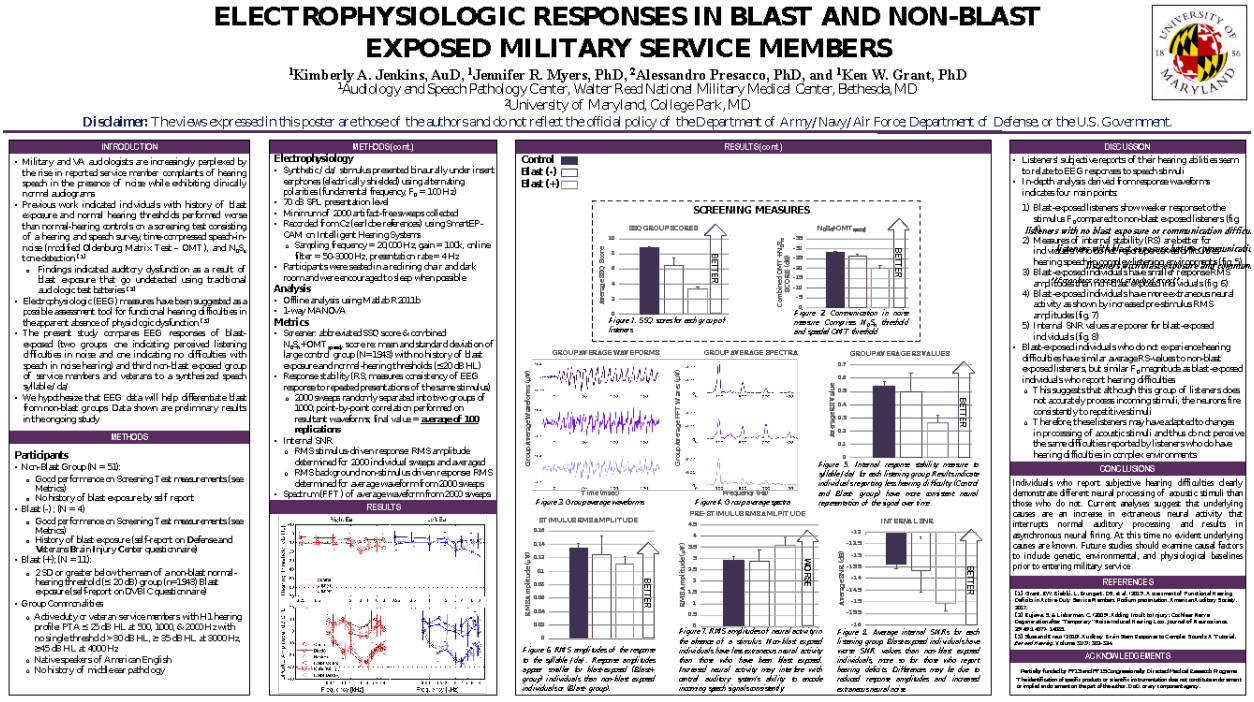
TITLE: Electrophysiologic (EEG) Responses in Blast and Non-Blast Exposed Military Service Members

AUTHORS (FIRST NAME, LAST NAME): *Kimberly A. Jenkins[1], Jennifer Myers[1], Ken W. Grant[1], Alessandro Presacco[2],*

INSTITUTIONS (ALL): *1. Walter Reed National Military Medical Center, Bethesda, MD*
2. University of Maryland, College Park, MD

Over the past decade military and VA audiologists have been perplexed by rises in service member complaints of difficulty hearing speech in the presence of background noise while exhibiting clinically normal audiograms. Previous work found that many listeners with normal to near-normal hearing thresholds exposed to blasts performed worse on a simple hearing screening test consisting of a six- question hearing and speech survey, time-compressed speech-in-noise, and N_0S_π tone detection. This indicates blast exposure in humans may cause auditory dysfunction undetected by traditional diagnostic hearing tests. Electrophysiologic measures are currently

being utilized to investigate auditory processing in blast- and non-blast exposed military personnel with normal-hearing thresholds. The stimulus consisted of a synthetic speech syllable (/da/). Comparisons of overall response amplitudes indicated decreased signal-to-internal noise ratio (SNR) in blast-exposed individuals. Detailed analyses revealed decreased stimulus response amplitudes and increased pre-stimulus response amplitudes in test subjects. Further, a measure of stimulus-driven response stability was poorer in blast-exposed individuals compared to controls. This suggests blast exposure causes increased extraneous neural activity that increases internal noise, reduces SNR, and impedes the auditory system's phase-locking ability. These changes in physiologic response properties observed through EEG recordings may help explain behavioral and subjective complaints in blast-exposed individuals.



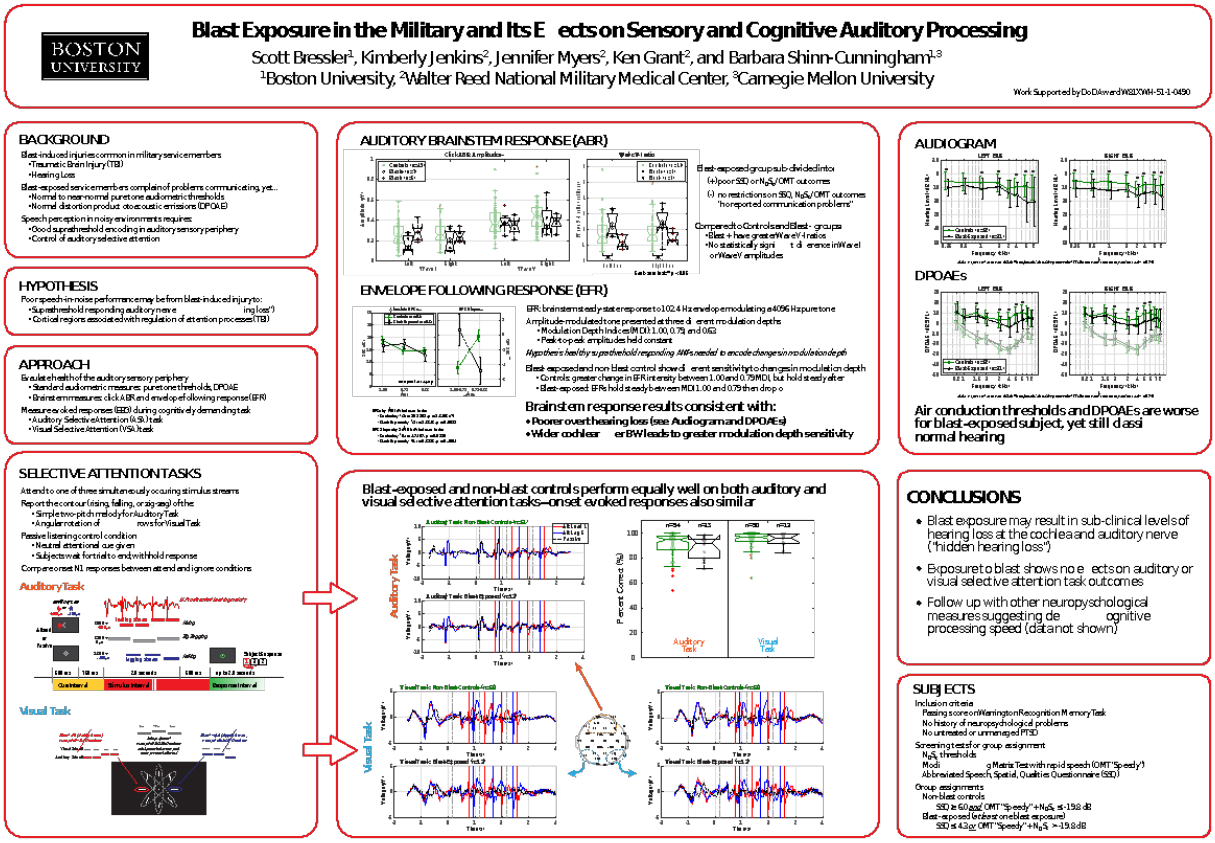
TITLE: Blast Exposure in the Military and Its Effects on Sensory and Cognitive Auditory Processing

AUTHORS (FIRST NAME, LAST NAME): *Scott Bressler[1], Kimberly Jenkins[2], Jennifer Myers[2], Kenneth Grant[2], Barbara Shinn-Cunningham[3]*

INSTITUTIONS (ALL): *1. Biomedical Engineering, Boston University, Boston, MA.*
2. Audiology, Walter Reed National Military Medical Center, Bethesda, MD.
3. Carnegie Mellon University, Pittsburgh, PA.

Blast-induced traumatic brain injury (TBI) and hearing loss are the two most common types of injuries sustained by military personnel while serving in the U.S. Global War on Terrorism. Recently several VA audiology clinics have reported active duty service members complaining of having problems communicating in noisy listening environments despite having normal to near-normal pure tone thresholds. In addition to traditional clinical measures, we used electroencephalography (EEG) to determine whether damage to suprathreshold responding auditory nerve fibers in the sensory periphery and/or trauma to cortical regions associated with attention and working memory were responsible for the reported listening complications. In separate auditory and visual selective attention tasks, behavioral and neural measures suggest no

evidence of long term neurotrauma affecting normal cognitive function. We found while absolute measures of auditory brainstem encoding varied greatly in all study subjects, comparisons of how the envelope following response (EFR) changes with modulation depth hint at differences between blast and non-blast exposed service members. These findings are consistent with audiometric threshold and distortion product otoacoustic emission data that show subtle differences between groups within clinically defined normal limits. Taken together these results suggest subclinical differences in audiometric measures might explain differences in suprathreshold listening.



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