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# Clinical Gaps-in-Noise Measures in Blast-Exposed Veterans: Associations with Electrophysiological and Behavioral Responses

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## ABSTRACT

It has been established that blast exposure and brain injury can result in self-reported and measured auditory processing deficits in individuals with normal or near-normal hearing sensitivity. However, the impaired sensory and/or cognitive mechanisms underlying these auditory difficulties are largely unknown. This work used a combination of behavioral and electrophysiological measures to explore how neural stimulus discrimination and processing speed contribute to impaired temporal processing in blast-exposed Veterans measured using the behavioral Gaps-in-Noise (GIN) Test. Results confirm previous findings that blast exposure can impact performance on the GIN and effect neural auditory discrimination, as measured using the P3 auditory event-related potential. Furthermore, analyses revealed correlations between GIN thresholds, P3 responses, and a measure of behavioral reaction time. Overall, this work illustrates that behavioral responses to the GIN are dependent on both auditory-specific bottom-up processing beginning with the neural activation of the cochlea and auditory brainstem as well as contributions from complex neural networks involved in processing speed and task-dependent target detection.

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It is estimated that approximately 26 million American adults complain of hearing difficulty and speech-in-noise (SIN) understanding problems despite having clinically normal hearing sensitivity (Beck et al. 2018). A recent survey of audiologists conducted by Koerner, Papesh, and Gallun (2020) revealed that many of these patients find their way to audiology clinics, with more than 68% of responding audiologists reporting seeing at least one normal-hearing patient per month who expressed hearing difficulties. Compared with the general population, military service members and Veterans may be more likely to develop functional hearing deficits due to several military-related risk factors such as blast exposure and head injury and risk of exposure to oto- and neurotoxicants, among others (Tepe et al. 2020). In fact, a recent prevalence estimate based on more than 3,400 participants revealed that approximately 33.6% of active-duty service members are at risk of functional hearing deficits despite having normal to near-normal hearing, with blast-exposed participants being 2.5 times more likely to experience subjective or objective deficits (Grant et al. 2021). Despite increasing awareness about the scope of this problem, clinical audiologists currently have few evidence-based guidelines for effectively assessing or managing functional auditory difficulties in normal-hearing patients. This lack of standardized clinical protocols largely stems from a gap in knowledge about the source of auditory difficulties in these normal hearing patients particularly as related to top-down versus bottom-up control of auditory processing and the potential for damage to non–auditory-specific structures that can impact auditory function.

Studies evaluating the auditory processing deficits associated with blast exposure in service members and Veterans reported the possibility of deficits in several domains including SIN understanding, binaural interaction and integration, temporal pattern recognition, sound localization, and temporal resolution abilities (Gallun et al. 2012, 2016; Kubli et al. 2018; Saunders et al. 2015). Although blast exposure is a leading cause of traumatic brain injury (TBI) among military personnel, growing evidence indicates that other TBI etiologies can also cause persistent auditory disabilities, even when the TBI is classified as mild (mTBI) (Bergemalm & Lyxell 2005; Hoover et al. 2014; Hoover et al. 2017; Oleksiak et al. 2012; Turgeon et al. 2011). Patterns of auditory processing deficits following blast exposure and other types of head injury are quite heterogenous across participants. However, loss of auditory temporal resolution, as revealed by poorer thresholds on the widely used clinical Gaps-in-Noise (GIN) test (Musiek et al. 2005b), is one of the most common findings among both military and civilian mTBI populations (Gallun et al. 2012, 2016; Hoover et al. 2017; Roup et al. 2020; Saunders et al. 2015). Poor auditory temporal resolution can negatively impact many other auditory functions including speech understanding in noise (Narne & Vanaja 2009; Rance et al. 2004; Rosen et al. 1992), and thus accurate assessment and treatment of temporal resolution deficits is fundamental to effective clinical care.

Temporal resolution requires a high degree of precise neural encoding between and within several levels of the auditory pathway (Baltus & Herrmann 2015), and neuroimaging work suggests these networks may be highly susceptible to damage from blast exposure and other types of mTBI. Though standard clinical imaging techniques are rarely sensitive to damage in cases of mTBI, more advanced techniques have revealed neural injuries that are often subtle, but also widespread. For instance, advanced diffusion tensor imaging techniques including fractional anisotropy and mean diffusivity have revealed that mTBI, including that from blast exposure, often results in diffuse axonal injuries (DAIs) as white matter tracts are stretched and sheared in response to external forces (Taber et al. 2015). As implied by the "diffuse"

moniker, axonal damage is frequently widespread and may affect areas including interhemispheric tracts, subcortical–cortical tracts, temporal lobe tracts, and frontoparietal tracts (Davenport et al. 2012; Niogi & Mukherjee 2010; Petrie et al. 2014; Taber et al. 2015). DAI damage can be observed in the brain even several years following the mTBI event (Inglese et al. 2005; Petrie et al. 2014), which may account for the chronic nature of auditory processing deficits in blast-exposed and mTBI patients (Gallun et al. 2016). Within the auditory brainstem, reduced volume within axonal fiber tracts may account for reports of poorer subcortical temporal responses to speech stimuli documented in athletes having sustained sports-related concussions (Kraus et al. 2016, 2017). However, GIN test responses appear to be even more sensitive to damage to auditory cortical regions compared with brainstem regions (Musiek et al. 2005b). The temporal cortex, which houses the auditory cortex, and the frontal cortex, which is heavily involved in executive function, are reported to be particularly susceptible to damage from mTBI due to bleeding, vascular dysregulation, and direct tissue damage as the soft tissues of the brain impact the skull (Levin & Kraus 1994). Blast exposure has been shown to lead to cortical thinning in the temporal, frontal, and insula regions (Tate et al. 2014), as well as scaring of brain tissue proximal to fluid-filled spaces and at the junctions between gray and white matter (Shively et al. 2016). Hence, several structures within the auditory pathway are at risk of damage that is likely to result in reduced temporal resolution.

The GIN test was specifically developed to serve as a rapid clinical measure of auditory temporal resolution (Musiek et al. 2005b). Listeners are presented with 6-second epochs of broadband noise which may contain anywhere between zero and three silent intervals, or "gaps." Gap durations vary between 2 and 20 ms, and listeners are asked to press a button immediately following detection of a gap. The left and right ears are typically tested independently as previous work indicates that thresholds may vary between the ears, possibly due to the presence of damage in different neural locations (Efron et al. 1985). The GIN has proven highly sensitive to the presence of a wide range of brain pathologies in various clinical populations (Chowsilpa et al. 2021), including individuals with blast exposure and mTBI (Gallun et al. 2012, 2016; Saunders et al. 2015), adults with mild cognitive impairment (Iliadou et al. 2017), those who stutter (Prestes et al. 2017), Parkinson's patients (Guehl et al. 2008), and patients with hippocampal sclerosis (Aravindkumar et al. 2012), among others. The range of pathologies associated with poor GIN performance likely reflects the diverse brain networks required to perform this task.

Indeed, while GIN performance clearly relies on intact and high functioning temporal resolution within the auditory pathway, performance is also dependent on the listeners' ability to attend to the auditory stimulus, their speed of information processing, and speed of motor response. The necessary involvement of non–auditory-specific brain functions required to complete the GIN test is likely a major reason that electrophysiological measures of temporal resolution targeting brainstem and auditory cortex do not always show a strong correspondence with behaviorally determined GIN thresholds (Bertoli et al. 2001, 2002; Werner et al. 2001). The recruitment of non-auditory networks during auditory perceptual tasks is certainly not specific to the GIN task. In fact, all other perceptual and behavioral processes such as speech understanding in noise and dichotic listening similarly depend on a range of sensory and cognitive functions, thus highlighting the non-modular nature of auditory processing in the brain (Musiek et al. 2005a). Behavioral measures of temporal resolution, including the GIN, provide an index of the true functional capacity of the brain by combining assessment of temporal acuity within the auditory pathway with assessment of the fidelity of additional non–auditory-specific neural networks required to support auditory processing and behavior.

The GIN represents a valuable clinical tool in the functional measurement of temporal resolution. However, being that it is not a "pure" measure of temporal resolution in the auditory pathway, it behooves clinicians and researchers utilizing the GIN to better understand the relationship between GIN performance and other non–auditory-specific

elements of auditory processing. In the present work, we sought to investigate the relationship between GIN performance and auditory processing functions at and downstream of the auditory cortex. Specific measures of interest included the N1 (N100) and P2 (P200) auditory evoked potentials (AEPs) generated by auditory cortical regions, the P3 (P300) auditory event-related potential generated in response to a simple tone-contrast oddball paradigm, and finally speed and accuracy of auditory information processing as indexed by reaction time and target detection accuracy, respectively, during the oddball target detection task. N1 and P2 responses are exogenous potentials in that they are primarily determined by the physical features of the auditory stimulus encoded and conveyed within the auditory pathway, though it is important to note that they may be mildly affected by attention (Näätänen & Teder 1991). In contrast, P3 measures are non–auditory-specific potentials elicited by endogenous task-dependent brain activity, especially the cognitive processes of attention and memory. For this reason, P3 measures are often referred to as cognitive event-related potentials that are dependent on activation of a diverse neural network involving regions of the neocortex, reticulothalamic pathways, and the limbic system, among others (Polich & Kok 1995). Hence, P3 latencies and amplitudes have been widely used as a neural index of selective attention and short-term memory in both normally functioning and impaired populations. Behavioral performance on the GIN task is governed by accurate encoding of auditory stimulus features, specifically rapid encoding of brief silent gaps in the noise background, as well as task-dependent demands including attention, rapid stimulus evaluation and discrimination, and motor response. Thus, comparison of GIN performance with exogenous N1 and P2 responses, endogenous P3 potentials, and information processing speed may shed light on whether some factors contribute more strongly to clinically measured GIN thresholds.

In the present study, behavioral performance and neural responses in a group of blast-exposed Veterans were compared with those obtained in a group of age- and hearing-matched control participants. Comparison of blast-exposed Veterans with control participants is likely to provide the wide range of responses needed to examine such relationships given that previous studies have shown that blast-exposed Veterans often perform poorly on the GIN (Gallun et al. 2012, 2016; Saunders et al. 2015), have generally less robust P3 responses to simple tone contrasts compared with earlier obligatory potentials (Gallun et al. 2012; Papesh et al. 2021), and have slower information processing speed (Clausen et al. 2021). We hypothesize that (1) GIN thresholds will not be strongly associated with either N1 or P2 cortical potentials that reflect only encoding within the auditory pathway or with response accuracy during the oddball detection task given the relatively simple nature of the pitch discrimination involved and (2) strong relationships will be found between GIN thresholds and measures reflecting processes including attention and task-dependent stimulus discrimination revealed by the P3 response and perceptual processing speed as measured by behavioral reaction times during the oddball detection task, as these measures more fully incorporate both neural encoding of stimuli within the auditory pathway as well as more generalized neural processing mechanisms that contribute to auditory behavioral function.

## METHODS

### Participants

Participants were recruited from flyers posted at the Portland VA Medical Center and via the NCRAR Subject Recruitment Database. Flyers sought the participation of Veterans who had been exposed to a high-intensity blast wave for a research study aimed to examine the effects of blast exposure on auditory function. Exclusionary criteria for all participants included pure-tone hearing thresholds greater than 30 dB hearing level (HL) at any test frequencies between 250 and 4,000 Hz; threshold differences of greater than 10 dB between the left and right ear at any test frequency; and diagnosis of schizophrenia, bipolar disorder, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, or any

neurological disorder not related to TBI sustained during deployment, or medical records indicating moderate or severe TBI (participants with diagnoses of mild TBI were permitted into the study). All potential participants completed an interview regarding their military service, prior head trauma, and blast exposure(s) including symptoms immediately after and within the first 24 hours of injury. Only participants who met basic criteria for mTBI established by the Defense and Veterans Brain Injury Center were admitted to the blast-exposed participant group based on symptoms immediately following the event including disorientation, ringing in the ears, nausea, light sensitivity, loss of consciousness not longer than 30 minutes, posttraumatic amnesia not more than 1 day, and/or headache. Participants in the control group were age-matched to those in the blast-exposed group and reported no history of blast exposure or any previous head injuries. This study was overseen by the Institutional Review Board of the Veterans Affairs Portland Healthcare System. All participants provided written informed consent prior to testing and were provided $20 per hour in compensation for participation.

## Self-Report Measures

Although a significant number of blast-exposed individuals report auditory difficulties, not all do (Gallun et al. 2016). Therefore, prevalence of self-perceived hearing difficulties in the current participant cohort was assessed using the Hearing Handicap Inventory for Adults (HHIA; Newman et al. 1990). The HHIA is a 25-item self-assessment scale designed to probe social and emotional aspects of hearing that affect daily life. Participants are given questions such as "Do you feel handicapped by a hearing problem?" and "Does a hearing problem cause you difficulty when listening to TV or radio?" and asked to respond with *Yes* (four points), *Sometimes* (two points), or *No* (zero points). Responses to each item are summed with possible scores ranging from 0 (no handicap) to 100 (total handicap). Scores of 0 to 16 indicate no hearing handicap, 18 to 42 indicate moderate hearing handicap, and scores of 44 or more indicate severe hearing handicap (Newman et al. 1991).

Blast-exposed Veterans have an increased risk of posttraumatic stress disorder (PTSD) which may contribute to hearing difficulties (Papesh et al. 2019) and impact cognitive functions including processing speed (Schuitevoerder et al. 2013). To assess the severity of symptoms associated with PTSD, participants completed the PTSD Checklist, Version 5 (PCL-5), a 20-item self-report measure containing indicators consistent with the DSM-5 criteria for PTSD (Blevins et al. 2015). Responders are asked to rate how bothered they have been by each item in the past month on a 5-point Likert scale ranging from 0 (not bothered at all) to 4 (extremely bothered). Responses are summed for a possible score range of 0 (no symptoms) to 80 (extreme symptoms). Scores of 33 and higher are suggestive of PTSD (Blevins et al. 2015).

## Behavioral Temporal Resolution Testing

Temporal resolution was measured using the GIN (Musiek et al. 2005b). Participants were presented with a series of 6-second segments of white noise that could contain anywhere from zero to three embedded silent gaps. Gaps durations of 2, 3, 4, 5, 6, 8, 10, 12, 15, and 20 ms were each presented a total of six times throughout presentations of the noise segments. Participants were instructed to respond immediately upon detecting a gap by pressing a button using whichever hand was most comfortable. Right and left ears were tested separately, starting with the right ear. Prior to testing, participants were given 10 practice items presented to the right ear with gap durations ranging from 10 to 20 ms for task familiarization. GIN thresholds were determined to be the shortest gap duration that a participant was able to detect in at least four out of six test presentations with all longer durations being detected during more than 50% of presentations. Thresholds of 8 ms and above indicate abnormally poor temporal resolution (Musiek et al. 2005b). Participants were tested using ER-3A insert earphones and stimuli were presented

through an audiometer at a level of 50 dB sensation level relative to the pure tone average at 500, 1,000, and 2,000 Hz in the test ear.

## Electrophysiology

The current study measured neural responses to a simple tone contrast. Stimuli consisted of an infrequently occurring 1,000 Hz "target" tone randomly interspersed within a sequence of frequently occurring 500 Hz "standard" tones. This simple tone contrast paradigm required a similar level of attention and basic stimulus discrimination as behavioral performance on the clinical GIN task. Each sequence consisted of 420 tones, with 80% being standard tones and the remaining 20% being randomly interspersed target tones. All stimuli were 100 ms in duration, including a 5-ms rise and fall and were presented at a level of 80 dB C through ER3A insert earphones (Etymotic Research) at an interstimulus interval of 1,500 ms. Participants were seated in a sound-attenuating booth during testing and were asked to relax, minimize eye and muscle activity, and press a button as soon as they detected a target tone using whichever hand was most comfortable for them. The left and right ears were tested separately, and the order of presentation was counter balanced across participants. Testing required approximately 10 minutes for each ear.

AEPs were obtained using a 64-channel cap (Electro-Cap International, Inc., Eaton, OH) connected to the Compumedics Neuroscan Synamps RT system (Charlotte, NC). The ground electrode was located on the forehead and Cz served as the reference electrode during neural recordings. Responses were analog low-pass filtered online at 100 Hz (12 dB/octave roll-off), and all channels were amplified and converted using an analog-to-digital sampling rate of 1,000 Hz. During offline processing, data re-referenced to an average reference of all electrodes, and eye movements were recorded and corrected using Neuroscan software. Responses were analyzed in 1,300-ms epochs consisting of a 200-ms prestimulus baseline and an 1,100-ms post-stimulus window. Off-line bandpass filters limited responses to between 0.1 Hz (high-pass filter, 24 dB/octave) and 30 Hz (low-pass filter, 12 dB/octave) to maximize cortical responses and reduce unwanted noise. Trials containing artifacts exceeding $\pm$ 100 V were rejected from averaging. For all individuals and conditions, 75% or more of the collected trials were available for averaging after artifact rejection resulting in an average of 69 averaged responses to target tones and 286 responses to standard (non-target) tones. P3 peak responses were measured at electrode Pz in response to target signals (Polich & Kok 1995), and N1 and P2 responses were measured at electrode Cz in response to standard stimuli (Näätänen & Picton 1987). Initial peak values were selected automatically based on the largest amplitude with the latency range of each individual peak. All peak values were then confirmed by an experienced experimenter via comparison with global field power traces and the participant's response to stimuli presented to opposite ear. Amplitude values were measured relative to the average amplitude of the 200-ms prestimulus baseline.

## Statistical Analyses

Independent two-tailed *t*-tests with equal variances not assumed were used to compare participant group differences related to ages, audiometric thresholds, HHIA, and PTSD screening results. Thresholds were compared between groups for each ear at all audiometric frequencies tested. Group and ear main effects and interactions on the GIN, N1, P2, and P3 amplitudes and latencies, and reaction times and percent correct measured during the P3 task were assessed using repeated measures ANOVA. Correlations between behavioral and electrophysiological measures were analyzed using Kendall rank correlation ($\tau_b$), as it is independent of underlying distributions and because the resulting significance values are more accurate in small sample sizes compared with other nonparametric measures such as Spearman's rho (Newson, 2002; Croux & Dehon, 2010). The Benjamini-Hochberg (B-H) procedure was used to limit the chance of Type I error in correlation analyses with the false discovery rate set to 0.1. This method of correction for multiple comparisons is more appropriate for evoked potential analyses then other methods such as Bonferroni, since evoked

potential components are not strictly independent of one another.

## RESULTS

### Participant Demographics

Table 1 shows the numbers, ages, and blast-exposure data associated with each participant group. All participants were male, reflecting the prevalence of males in the Veteran population. Although the average age of participants in the control group was slightly higher, this difference was not significant ($t_{(17.751)} = -0.602$; $p = 0.553$). Average pure-tone hearing thresholds for each group are shown in Fig. 1. Though blast-exposed participants had slightly poorer thresholds at 6,000 and 8,000 Hz, only thresholds in the left ear at 8,000 Hz differed significantly between groups ($t_{(22.991)} = 1.696$; $p = 0.034$).

**Table 1 Characteristics of the blast-exposed and control group participants**

| | Blast | Control |
|---|---|---|
| Number | 16 | 9 |
| Mean age in years (SD) | 36.9 (12.1) | 39.9 (11.2) |
| Age range | 24–58 | 25–58 |
| Average no. of blast exposures | 7.5 | 0 |
| No. of blast exposure range | 1–40 | 0 |
| Years since most severe exposure (SD) | 7.5 (2.1) | 0 |

### Subjective Reports of Hearing Handicap and PTSD symptoms

Blast-exposed participants reported significantly more perceived hearing handicap (average HHIA score of 32.5; SD of 31.3) compared with control participants (average HHIA score of 6; SD of 12.2; $t_{(21.256)} = 3.004$ $p = 0.007$). Six of the 16 blast-exposed participants indicated that they had severe hearing handicap (scores $> 42$) with an additional two blast-exposed participants rating themselves as moderately handicapped (scores between 17 and 42). In contrast, only two control participants considered themselves to have a moderate hearing handicap, and none indicated a perceived severe handicap. Results of the PTSD checklist also revealed significant group differences ($t_{(21.735)} = 3.605$ $p = 0.002$) with blast-exposed participants reporting greater symptoms consistent with PTSD (average score of 9; SD of 4.8) compared with controls (average score of 3.1; SD of 3.3).

### Behavioral GIN Data

Using a normative cut-off of 8 ms (Musiek et al., 2005a; Musiek et al., 2005b) such that thresholds of less than 8 ms were considered normal, only three blast-exposed participants performed in the normal range in both ears, while eight performed in the abnormal range in both ears, and the remaining four blast-exposed participants failed testing in one ear but passed the other (three failed in the left ear only, one in the right ear only). Average GIN thresholds for the blast-exposed group were 7.1 ms (SD: 2.4 ms) in the right ear and 7.9 ms (SD: 2.1 ms) in

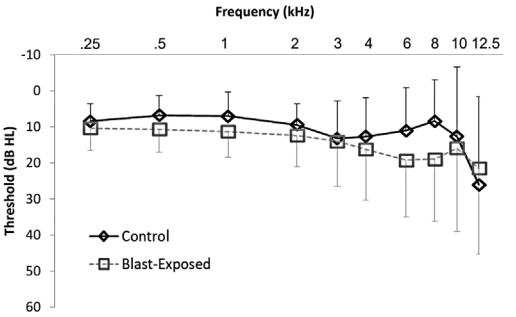


**Figure 1** Average pure tone audiometric thresholds for the blast-exposed and control participant groups. Error bars represent ± 1 SD.

the left ear. Among the control participants, three fell into the abnormal range in one ear (two in the left ear, one in the right ear) and all others had thresholds within the normal range. The average GIN threshold for control participants was 4.6 ms (SD: 1.6 ms) in the right ear and 5.6 ms (SD: 1.7 ms) in the left ear. Overall, blast-exposed participants had significantly poorer GIN thresholds compared with control participants as evidenced by a significant main effect of group ($F_{(1,22)} = 9.415$; $p = 0.006$). A significant main effect of ear was also observed with participants having better (lower) thresholds in the right ear compared with the left ear ($F_{(1,22)} = 4.932$; $p = 0.037$), though no interaction between group and ear was found ($F_{(1,22)} = 0.128$; $p = 0.724$).

## N1 and P2 Responses

The top panels of Fig. 2 show the grand average waveforms for both the control and blast-exposed participant groups in response to the non-target 500-Hz tones presented to the left and right ear. Responses of blast-exposed participants are shown with solid black lines, and those of controls are shown in broken gray lines. N1 and P2 responses are labeled on the left panel. Average latency and amplitude of N1 and P2 responses for each group and results of statistical analyses are shown in Table 2. N1 latencies were similar between the groups, with no significant main effects or interactions found. However, a significant interaction between group and ear was found for N1 amplitudes such that blast-exposed participants had larger responses than control participants when stimuli were presented to the right ear, but similar response amplitudes when presented to the left ear. For P2 peaks, a significant main effect of group was found for P2 latencies, with blast-exposed participants' responses peaking significantly earlier compared with control participants. Although P2 response amplitudes appeared to be somewhat larger for control participants compared with blast-exposed participants, particularly for left ear presentations, this effect was not significant. No main effects or interactions of Group or Ear were significant for P2 amplitudes.

## P3 Responses

The bottom panels of Fig. 2 show the grand average waveforms for both the control and blast-exposed participant groups in response to the target 1,000-Hz tones presented to the

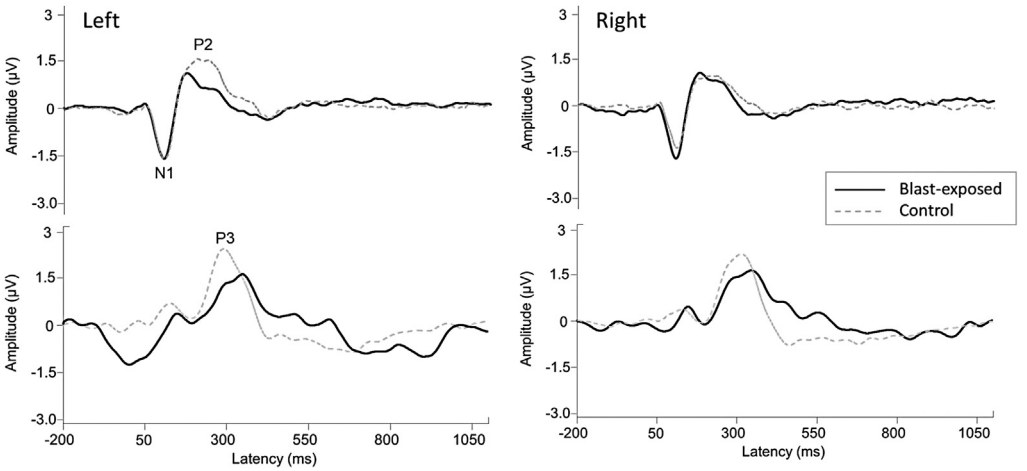


**Figure 2** Grand averaged auditory evoked potential responses for the blast-exposed (solid black lines) and control (broken gray lines) participant groups. The top panels represent responses to the standard 500-Hz stimulus with N1 and P2 peaks labeled in the left panel, and the bottom panels represent responses to the target 1,000-Hz stimulus with the P3 peak labeled in the left panel. Responses to stimuli presented to the left ear are shown on the left side and responses to stimuli presented to the right ear are shown on the right.

**Table 2 Descriptive and repeated-measure ANOVA statistics**

| | N1 | | P2 | | P3 | | | |
|---|---|---|---|---|---|---|---|---|
| | **Amplitude** | **Latency** | **Amplitude** | **Latency** | **Amplitude** | **Latency** | **% Correct** | **Reaction time** |
| Left ear | | | | | | | | |
| Blast-exposed | −1.73 (0.56) | 104 (9) | 1.38 (0.7) | 186 (25.6) | 2.87 (1.32) | 342.4 (38.7) | 92.8 (14.5) | 0.435 (0.113) |
| Control | −1.8 (0.69) | 104.4 (14.2) | 2.01 (1.05) | 210.9 (23.8) | 3.04 (1.08) | 295.7 (26.4) | 95.1 (8.4) | 0.342 (0.081) |
| Right ear | | | | | | | | |
| Blast-exposed | −1.96 (0.43) | 105.5 (7.2) | 1.38 (0.67) | 189.1 (21.3) | 2.58 (1.24) | 328.4 (37.1) | 93 (11.3) | 0.421 (0.118) |
| Control | −1.47 (0.81) | 103.3 (14.2) | 1.29 (0.66) | 218 (33.5) | 3.15 (1.5) | 303.4 (33.6) | 95.7 (8.8) | 0.34 (0.064) |
| ANOVA | | | | | | | | |
| Group | $F = 0.909$; | $F = 0.045$; | $F = 1.095$; | **$F = 9.934$;** | $F = 0.581$; | **$F = 8.121$;** | $F = 0.338$; | **$F = 4.345$;** |
| | $p = 0.350$ | $p = 0.834$ | $p = 0.306$ | **$p = 0.004$** | $p = 0.454$ | **$p = 0.009$** | $p = 0.567$ | **$p = 0.049$** |
| Ear | $F = 0.171$; | $F = 0.012$; | $F = 4.001$; | $F = 0.638$; | $F = 0.170$; | $F = 0.160$; | $F = 0.041$; | $F = 0.665$; |
| | $p = 0.683$ | $p = 0.913$ | $p = 0.057$ | $p = 0.433$ | $p = 0.684$ | $p = 0.693$ | $p = 0.841$ | $p = 0.424$ |
| Group × Ear | **$F = 6.077$;** | $F = 0.548$; | $F = 3.889$; | F = 0.097; | $F = 0.793$; | $F = 1.983$; | $F = 0.006$; | $F = 0.333$; |
| | **$p = 0.022$** | $p = 0.466$ | $p = 0.061$ | $p = 0.759$ | $p = 0.382$ | $p = 0.172$ | $p = 0.941$ | $p = 0.570$ |

Abbreviations: ANOVA, analysis of variance.
Note: Amplitude measures are reported in microvolts. Latency and reaction time measures are reported in milliseconds.

left and right ear. P3 peaks are labeled in the left panel. Table 2 shows the average latency and amplitude of P3 responses, percent correct target detection, and reaction time for each group as well as the results of statistical analyses. Blast-exposed participants generally had smaller amplitude and longer latency responses compared with control participants. However, only differences in latency were found to be significant as evidenced by a main effect of Group. Neither significant main effects of Ear nor significant interactions between Group and Ear were found for either P300 response latencies or amplitudes.

Accuracy of target detection was excellent for both participant groups with average percent correct of more than 92% of targets for both left and right ear conditions. Control participants were slightly, though not significantly, more accurate compared with blast-exposed participants. Despite similar levels of accuracy, control participants were able to detect targets significantly faster than their blast-exposed counterparts (Table 2).

## Correlations between GIN and Electrophysiological Data

Correlations were examined between right and left ear GIN thresholds and the following measures: N1, P2, and P3 latencies and amplitudes presented to each ear, reaction times on the P3 task for both right and left ear presentations, and scores on the HHIA and PTSD screener. Correlations were also assessed between the HHIA and PTSD screener with N1, P2, and P3 latencies and amplitudes presented to each ear and reaction times on the P3 task for both right and left ear presentations. Hence, a total of 28 correlations were measured. To reduce the chance for type-I errors, the Benjamini-Hochberg correction was applied using a 10% false discovery rate. Resulting significant correlations are plotted in Fig. 3 and associated statistical measures, including $\tau_b$ and $p$ values, are provided in Table 3. Poorer left ear GIN thresholds were associated with longer P3 latencies for left and right ear presentations (Fig. 3A, D, respectively), as well as smaller N1 amplitudes (Fig. 3B) and longer reaction times (Fig. 3C). No significant correlations

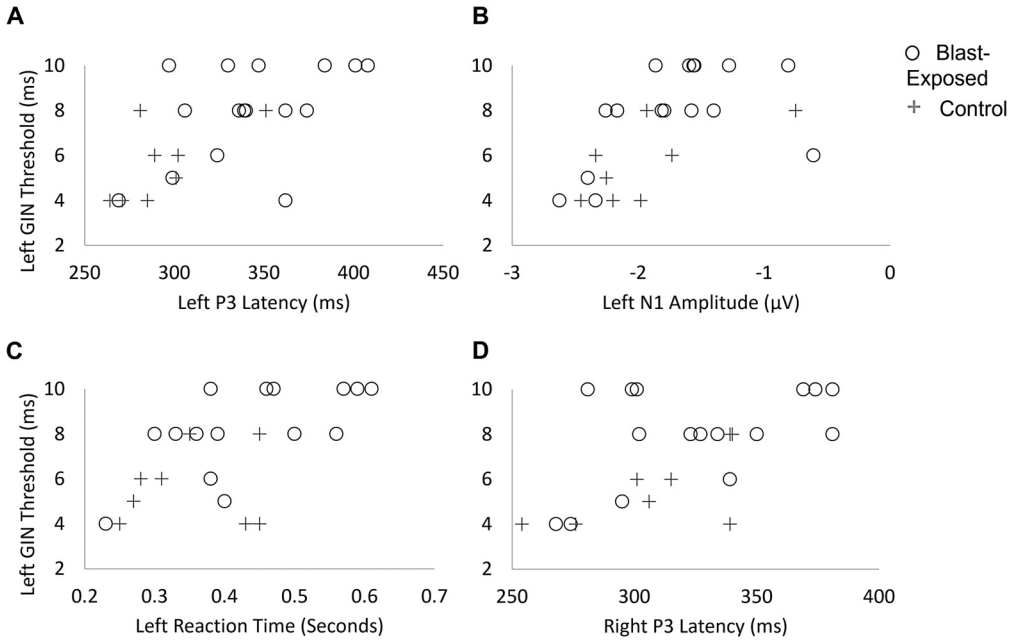


**Figure 3** Scatter plots of all significant correlations identified. Significant correlations include left ear GIN behavioral thresholds with P3 latencies in response to left ear presentations (**A**), amplitude of N1 responses to left ear presentations (**B**), reaction time to target stimuli presented to the left ear (**C**), and P3 latencies in response to right ear presentations (**D**). Responses from blast-exposed participants are represented as circles and responses from control participants are shown as plus signs.

**Table 3 Significant results of Kendall rank correlation analysis**

| | *p*-Value | $\tau_b$ | B-H critical value |
|---|---|---|---|
| GIN (left) × P3 latency (left) | 0.001 | 0.538 | 0.007 |
| GIN (left) × N1 amplitude (left) | 0.001 | 0.517 | 0.013 |
| GIN (left) × reaction time (left) | 0.003 | 0.489 | 0.020 |
| GIN (left) × P3 latency (right) | 0.003 | 0.468 | 0.027 |

Abbreviations: GIN, Gaps-in-Noise; B-H, Benjamini-Hochberg.

were found between GIN thresholds in the right ear and any electrophysiological or reaction time measures, and neither HHIA nor PTSD screening results were correlated with any other test measures.

## DISCUSSION

The present work evaluated the relationship between behavioral GIN thresholds, N1, P2, and P3 electrophysiological measures, and behavioral measures of reaction time and response accuracy in a simple pitch-based oddball paradigm. Because the behavioral responses provided on the GIN test necessarily require the activation of non–auditory-specific pathways that are nonetheless critical to auditory processing, such as attention and perceptual processing speed, we hypothesized that strong associations would be found between GIN scores and cognitive measures including the P3 and reaction time during the oddball task, the latter of which served as an estimate of information processing speed. Exogenous cortical responses to a simple pure-tone stimulus were not predicted to reflect temporal processing mechanisms required for the GIN; therefore, significant relationships were not expected between GIN scores and N1 or P2 responses. Overall, our results provide additional support for the negative effects of blast exposure on auditory function, as evidenced by significantly greater reports of hearing difficulties, poorer GIN thresholds, longer P3 latencies, and longer response times in blast-exposed participants compared with controls (Table 2). As hypothesized, significant correlations were found between GIN scores and P3 measures as well as reaction time measures. However, in contrast to our predictions, N1 response amplitude was also found to be significantly correlated with GIN scores. Finally, ear-specific GIN test results proved to be important for providing cohesion among the different test measures. Not only GIN thresholds in the left ear were poorer across all participants regardless of group, but it was these poorer thresholds that resulted in each of the significant correlations found in the present study (Fig. 3; Table 3). The following is a discussion of how these results may inform use and interpretation of the GIN test and suggestions for future research.

### GIN and Cortical Responses

The present study found a significant Group difference on obligatory cortical evoked potentials (Table 2). Specifically, P2 response latencies were shorter for blast-exposed participants compared with controls for both right and left ear presentations, and N1 amplitudes were significantly larger (more negative) for blast-exposed Veterans for right ear presentations. While at first these results may seem surprising given the arguments in favor of widespread neural damage following blast exposure, several lines of evidence indicate that blast-related head injury leads to hyperexcitability of cortical sensory regions due to dysregulation of the normal inhibitory control of excitatory activity (Hsieh et al., 2017; Guerriero et al., 2015; Carron et al., 2016). Within the auditory cortex, blast exposure has been shown to lead to disruptions in cortical tonotopic maps and broadening of the receptive fields of auditory cortical neurons (Masri et al. 2018), as well as increases in auditory cortical neuron spontaneous activity rates and increased bursting activity (Luo et al. 2017). There is limited electrophysiological evidence of cortical hyperexcitability in patients with mTBI. For example, studies of both civilian (Arciniegas et al., 2000) and blast-exposed Veterans (Papesh et al. 2019) with prior mTBI have shown poor sensory gating, the process by which preattentive brain networks filter incoming sensory information for novelty and

relevance while habituating response to irrelevant or repetitive information (Grunwald et al. 2003). One previous study of blast-exposed participants' N1 and P2 responses to tones presented during an oddball task demonstrated P2 latency effects similar to the current study (Papesh et al. 2021), while another showed no effects of participant group P2 responses but reduced N1 response amplitudes in one ear (Gallun et al. 2012). Still, neither P2 response latencies nor N1 amplitudes to right ear stimulation were associated with GIN scores, suggesting that if hyperexcitability is present within the auditory cortex, it is not related to GIN performance in the present study cohort. Rather, it is notable that a significant correlation was found between the amplitude of the N1 response in the left ear and GIN scores in the left ear (Table 3) such that larger (more negative) amplitudes were associated with better (smaller) GIN thresholds (Fig. 3B). Similar to performance on the GIN task, N1 and P2 measurements were conducted using an active listening paradigm in the current study. Although N1 and P2 are predominantly obligatory exogenous potentials dependent on stimulus characteristics, attention to auditory stimuli has been previously shown to produce small but significant increases in the amplitude of N1 responses (Thornton et al. 2007). Thus, the influence of attention in the association between GIN thresholds and N1 amplitudes cannot be ruled out in the current paradigm. Still, we hypothesized that no significant relationship would be found between GIN thresholds and these early, exogenous neural responses because, despite auditory temporal precision clearly relying upon high fidelity of encoding in the auditory pathway, behavioral tasks such as the GIN necessarily recruit additional neural pathways involved in stimulus comparison and information processing speed that are not reflected by obligatory evoked potentials. However, the current finding suggests that the strength of neural representation of stimuli within the auditory cortex plays a significant role in dictating behavioral gap detection responses as later downstream cognitive processes acting upon those representations.

## GIN and P3 responses

Compared with control participants, blast-exposed participants had significantly poorer GIN thresholds and longer P3 latencies (Table 2). Both of these findings are in line with previous work reporting the effects of blast exposure and mTBI on behavioral measures of temporal processing (Gallun et al. 2016; Hoover et al. 2017; Saunders et al. 2015) as well as P3 measures in response to simple tone contrasts (Gallun et al. 2012; Nandrajog et al. 2017; Papesh et al. 2021). Blast-exposed participants were able to perform the two-tone discrimination task with the same level of accuracy as their non–blast-exposed counterparts (Table 2). However, they had significantly longer response times, suggesting that they took longer to process the pitch difference between stimuli and provide a behavioral response.

As hypothesized, significant correlations were found between GIN thresholds P3 latencies and reaction times (Table 3), with poorer GIN scores corresponding to longer P3 latencies (Fig. 3A, D) and increased reactions times (Fig. 3C). While the GIN and the P3 oddball tasks measure different auditory processes (temporal resolution and pitch discrimination, respectively), both have important similarities that likely contributed to the significant associations. Both are essentially target detection tasks that require considerable attention and vigilance, depend on the speed of evaluation and discrimination of stimuli within the constructs of the specific task, and require a rapid behavioral response. Given these similarities, there is likely to be significant overlap in the neural pathways that dictate responses to GIN stimuli and P3 responses to target tones. P3 responses are called "cognitive" or "endogenous" event-related potentials in that they correspond to coordinated activation of wide networks within the brain in response to specific task demands as opposed to obligatory sensory evoked potential responses which are largely dictated by exogenous stimulus-related factors. While this makes specifying the exact neural generators of ERPs difficult, several converging lines of research suggest that the P3 arises from contributions of the reticular formation, lemniscus, inferior colliculus, thalamus, primary

auditory cortex, frontal cortex, centro-parietal cortex, and the hippocampus (Linden 2005; Polich 2007). The P3 potential reflects a stage of information processing associated with an attention-driven comparison process that is distinct from earlier stages of stimulus feature mismatch detection in the auditory pathway (Polich 2007). As such, P3 latencies provide an important objective measure of information processing speed, particularly given that a meta-analytic review of chronic symptoms after mTBI found that slower processing speed was the most influential factor in accounting for a wide range of neuropsychological deficits including attention, working memory, and adaptive and executive functioning (Frencham et al. 2005).

The neurophysiological tests with which P3 latencies are most closely associated are those that measure working memory and the speed attentional resource allocation (Polich & Kok 1995). As such, P3 measures are believed to be sensitive to even subtle cognitive impairments, including those stemming from DAI (Gaetz & Bernstein 2001). Hence, the longer P3 latencies measured in blast-exposed participants in the present work likely reflect mTBI-related effects including slower attentional resource allocation and reduced working memory. Both the P3 task and GIN performance require attention as well as working memory in that both involve understanding, recalling, and responding in a specific way depending on the analysis of the stimuli presented. The significant correlation between GIN thresholds with P3 latencies and reaction times thus indicates that the GIN is likely tapping into elements of stimulus evaluation, attention, and working memory that underlie behavioral auditory processing and that depends on activation of a widespread neural network that includes both auditory and non–auditory-specific regions.

Still, it is important to note that P3 responses and reaction time are also affected by the salience of the contrasts between stimuli in the oddball paradigm (Polich et al. 1996). Thus, it is possible that the significant association between GIN scores and P3 responses is in part a reflection of how robustly stimulus features are represented at the level of the auditory cortex, as suggested by the significant relationship between GIN scores and N1 amplitudes. Another line of evidence supporting this possibility comes from studies of adult patients with mild to moderate stuttering. Previous studies have revealed poorer gap detection thresholds (Prestes et al. 2017), and less robust N1, P2, and P3 latencies (Hampton & Weber-Fox 2008; Prestes et al. 2017) among people who stutter compared with those who do not, leading researchers to theorize that people who stutter require more time to elicit the P3 component, possibly due to poorer representation of auditory stimuli within the auditory pathway. In addition, examination of P3 measures in combination with neuropsychological testing in patients has not always shown correspondence between P3 measures and cognitive functioning such that P3 measures may remain prolonged, while behavioral measures of cognition show recovery to normal levels (Nandrajog et al. 2017). Future work exploring the relationship between P3 responses with earlier brainstem and cortical evoked potentials is warranted to help tease apart the effects of deficits in sensory encoding versus information processing on P3 responses and GIN thresholds, including utilization of more complex evoked potential paradigms that further stress temporal encoding within the auditory pathway.

### Right versus Left Ear Presentation

An intriguing, and unexpected, finding in these results was that only GIN thresholds in the poorer ear (the left ear in this cohort) were significantly correlated with any other test measures (Fig. 3; Table 3). Although blast-exposed Veterans had overall significantly poorer GIN thresholds compared with controls, both groups demonstrated significantly poorer thresholds in the left ear compared with the right ear. This result was unexpected but could be due in part to the fact that all participants were presented with the GIN in the right ear first followed by the left ear. Thus, while it is possible that the ear differences here are due to chance differences in this particular cohort of participants, it is also possible that listening fatigue may have affected performance during left ear GIN assessment in both listener groups. The GIN is normally presented to each ear

separately based on the idea that damage in one hemisphere is more likely to affect scores for stimuli presented to the contralateral ear (Efron et al. 1985), and normative data for this test are based on monaural presentation (Musiek et al. 2005b). However, most studies indicate no significant differences between GIN thresholds for the two ears, even in patients with known neural pathologies (Filippini et al. 2020). This may lead some to present the GIN test binaurally, particularly in clinical situations when testing time is at a premium. However, the present results reveal that deficits which are likely to impact overall auditory function may be missed if each ear is not measured independently. Particularly since the brain relies upon precise temporal encoding from both ears to perform important tasks such as sound localization and spatial release from masking, our results argue in favor of monaural assessment of the GIN to allow for detection of those cases in whom temporal processing is not equal between the ears.

## Self-Report Measures: HHIA and PTSD

Consistent with previous reports (Gallun et al. 2016; Saunders et al. 2015), blast-exposed Veterans reported significantly higher levels of perceived auditory disability compared with control participants despite having good hearing sensitivity. Higher failure rates on the GIN and longer P3 latencies and reaction times in the blast-exposed cohort likely indicate that poorer neural perceptual information processing contributes to these perceived symptoms. However, no significant correlation was found between self-report and either behavioral or neural indices of auditory function. This situation is surprisingly common (Saunders, 2009) and may be related to differences in auditory performance achieved in a controlled testing environment with well-controlled stimuli versus those achievable in a complex real-world setting.

There is a high association between mTBI and PTSD among blast-exposed military service members (Stein et al., 2019). Multiple symptoms overlap between these two conditions, making teasing apart the effects of one from the other difficult. In fact, some researchers suppose that the majority of postconcussive syndrome symptoms may be more related to persistent PTSD rather than neural effects of mTBI (Hoge et al., 2008). For example, both conditions may result in fatigue, irritability, poor sleep, and cognitive effects on attention and memory (Grandhi et al. 2017). Within the auditory domain, PTSD diagnoses are associated with poor habituation to sound and reduced understanding of rapidly spoken speech (Papesh et al. 2019), reduced auditory gating (Neylan et al. 1999), increased physiological response magnitude to acoustic startle stimuli (Shalev et al. 2000), and even auditory hallucinations (Mueser & Butler 1987). Blast-exposed participants in the current study reported significantly higher levels of PTSD symptoms compared with control participants, although scores on the PTSD Checklist were not found to be associated with any of our test measures. This could potentially be because PTSD symptoms do not affect temporal processing or two-tone discrimination. It could also be that auditory testing conducted in the current paradigm—simple tones and noises measured in a quiet secure sound booth—is unlikely to stimulate symptoms of PTSD.

## Limitations

The present work represents a novel exploration of relationships between neural sensory or cognitive processing mechanisms and behavioral temporal resolution based on a relatively small sample size of blast-exposed and control participants. As such, additional work involving larger sample sizes is needed prior to extrapolating these conclusions to the general population. In addition, this work used a simple oddball pitch discrimination task to record N1, P2, and P3 measures. Future work should explore relationships between behavioral temporal resolution and neural coding using a purely passive paradigm to elicit the N1 and P2 response and a more complex P3 oddball paradigm, ideally one that measures temporal resolution, to increase cognitive load and better align with the behavioral measure of interest. Furthermore, additional information could be gained from using a standardized cognitive measure to corroborate measures of processing

speed or other cognitive domains such as working memory or attention. It is also notable that a significant group difference was found on the PTSD severity index, and thus it is likely that both neural damage from blast exposure as well as neurological changes related to PTSD symptoms are likely to contribute to the results found here as well as the greater perceived handicap reported among blast-exposed participants.

## SUMMARY AND CONCLUSIONS

Overall, our results provide additional support for the notion that blast exposure can result in long-lasting auditory dysfunction measurable using self-report, behavioral auditory processing, and neural processing indices. Significant differences found between right and left ear GIN thresholds across all participants, coupled with the finding that GIN thresholds in the poorer ear were associated with several other auditory information processing stages, argues in favor of continued monaural testing of the GIN even among patients without known neural pathologies. The significant correlations found between GIN scores and both exogenous and endogenous cognitive responses reveal the importance of robust encoding of stimulus features within the auditory pathway as well as perceptual information processing speed regulated by non–auditory-specific networks within the brain. Further work is needed to determine the extent to which poor neural encoding within the auditory pathway may affect later cognitive potentials and behavioral responses in normally hearing listeners with auditory complaints.

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### CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

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