Blast Exposure Disrupts Tonotopic Frequency Map in the Primary Auditory Cortex

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ABSTRACT

Blast exposure can cause various auditory disorders including tinnitus, hyperacusis, and other central auditory processing disorders. While this is suggestive of patholologies in the central auditory system, the impact of blast exposure on central auditory processing remains poorly understood. Here we examined the effects of blast shockwaves on acoustic response properties and frequency mapping in auditory cortex. We found that multiunits recording from the auditory cortex exhibited higher acoustic thresholds and broader frequency tuning in blast-exposed animals. Furthermore, there was distorted frequency mapping in primary auditory cortex. These changes may contribute to central auditory processing disorders.

KEYWORD: blast, auditory cortex, frequency map, central auditory processing disorder,

INTRODUCTION

Exposure to blast shockwaves can cause sensory and neurological disorders in the auditory system, such as hearing loss, tinnitus, hyperacusis and central processing disorder (Jury and Flynn, 2001; Rossiter et al., 2006; Sayer et al., 2008; Belanger et al., 2009; Mao et al., 2012; Remenschneider et al., 2014; Saunders et al., 2015; Bressler et al., 2017; Ouyang et al., 2017). However, the mechanism by which blasts impact the auditory system remains unclear (Rosenfeld and Ford, 2010). Exposure to shockwaves causes damage to the ear, but the impact can be quite different from that of noise exposure (Bauer et al., 2008). Blast shockwaves are brief and often rupture the tympanic membrane, which decouples the inner ear from further mechanical over-stimulation (Xydakis et al., 2007). Consequently, blast exposure often causes severe acute hearing loss, but only mild long-term hearing loss following recovery of the tympanic membrane (Mao et al., 2012; Chen et al., 2013; Saunders et al., 2015; Bressler et al., 2017). By contrast, exposure to loud noises typically does not rupture the tympanic membrane, meaning that mechanical over-stimulation of the inner ear can be sustained, potentially resulting in more long-term hearing loss (Yang et al., 2011). Therefore, damage to hair cells, spiral ganglion neurons, and the central auditory pathway resulting from these distinctly different auditory traumas may vary greatly (Luo et al., 2014a, b; Niwa et al., 2016; Luo et al., 2017).

In addition to hearing loss, blasts cause traumatic brain injury (TBI) and may introduce additional pathologies to the central auditory pathway (Kamnaksh et al., 2011; Mao et al., 2012; Valiyaveettil et al., 2012; Tate et al., 2014; Race et al., 2017). Solid body structures, such as the brain, were previously considered to be at low-risk of sustaining shockwave injury (Argyros, 1997; Elsayed, 1997; Stuhmiller, 1997; Cernak et al., 2001). However, subsequent studies have

revealed a wide range of cellular injuries and inflammatory responses that occur despite a lack of hemorrhage or gross brain damage (Cernak et al., 2001; Sajja et al., 2012; Abdul-Muneer et al., 2013; Arun et al., 2013). For example, shockwaves from a single blast can compromise the membranes of neural and glial cells, allowing intracellular proteins to leak into cerebrospinal fluid (Saljo et al., 2003; Leung et al., 2008). Likewise, shockwave exposure activates resident microglia and astrocytes within 30 minutes (Kaur et al., 1995; Cernak et al., 2001; Saljo et al., 2001; Svetlov et al., 2010; Cernak et al., 2011; Du et al.) Activated microglia subsequently release TNF-α and other pro-inflammatory cytokines, generating both acute and chronic cellular inflammatory responses (Garden and Moller, 2006).

Here we examine the effects of blast shockwave exposure on auditory frequency mapping in the primary auditory cortex (AI) of the rat. We found that blast exposure resulted in distorted frequency mapping with over-representation of seemingly random narrow frequency ranges.

MATERIAL AND METHODS

Animals. All procedures used in this study were approved by the Animal Care and Use Committees at the University of Arizona and Wayne State University. Ten Sprague-Daley rats, male and 2-months old, were purchased from Charles River and used in this study. Five were chosen randomly and assigned to the blast-exposed group and the remaining five rats were assigned to the sham-exposed group.

Blast exposure and behavioral tests. Blast exposure was performed as described before (Mao et al., 2012). The rat was anesthetized with isoflurane (0.75-1% in a 2:1 N_2O:O_2 gas mixture). The

right ear was protected with an earplug and sealed with mineral oil. Each rat was exposed to a single 22-psi blast using a custom-built shock-tube assembly (ORA, Inc.). Blast exposure at this level does not affect rats' eating and drinking behaviors. The pressure waveform was monitored using piezoelectric sensors (PCB Piezotronics). A high-speed video camera (HG100K, Kodak), which captures up to 3000 frames/s, was used to monitor the animal's orientation and movement, prior to, during, and after delivery of the pressure wave. Sham-exposed animals underwent the same procedure without blast delivery.

Electrophysiological Recording Procedure. AI in control and blast-exposed rats was mapped as previously described (Kim and Bao, 2009). Rats were anesthetized with isoflurane (1-3%), and placed on a homeothermic heating pad at 36.5 °C (Harvard Apparatus) in a sound attenuation chamber. The head was secured with a custom head-holder that left the ears unobstructed. The right auditory cortex was exposed and kept under a layer of silicone oil to prevent desiccation. Multi-unit activity was evenly sampled from AI. AI can be identified by its tonotopic orientation—higher frequencies are represented in a more rostral and dorsal position compared to the caudally represented lower frequencies. Adjacent cortical auditory fields have different tonotopic orientations (Guo et al., 2012). The border of AI was defined by unresponsive sites or sites with CFs that were incongruent with the AI tonotopic gradient. As blast-exposed animals tended to have incomplete representations of low and high frequencies (Figure 1), we carefully searched for those representations near the rostral and caudal ends of AI in both blast-exposed and sham-exposed animals. Neural responses were recorded using tungsten microelectrodes (FHC) at a depth of 400-450 microns, presumably from the thalamorecipient layer. Responses to 25-ms tone pips (4-ms $\cos^2$ ramp) of 41 frequencies (2 to 32 kHz, 0.1 octave spacing) and eight

sound pressure levels (10–80 dB, 10-dB steps) were recorded three times per stimulus (i.e., a frequency-intensity combination) to reconstruct the frequency-intensity receptive field. A TDT coupler model electrostatic speaker was used to present all acoustic stimuli into the left ear (contralateral to the recorded cortical hemisphere). All frequency-by-intensity combinations were repeated 3 times.

An AI map was constructed from 19 to 46 multiunits from within AI (33 ± 5 sites, n = 10, mean ± SEM; please see Figure 1 for examples) out of a total of 40 to 68 multiunits that were recorded (54 ± 5 sites, n = 10, mean ± SEM) from each animal. When encountered, additional non-responsive sites were marked on the cortical image to help define the boundary of AI, without recording a receptive field.

Data Analysis. The receptive fields and response properties were calculated using custom MATLAB programs as reported before (Yang et al., 2014). The three repetitions per stimulus are not sufficient to determine statistically whehter a multiunit responded to a particular frequency-intensity combination. Therefore, we based our analysis on the entire receptive field, which was reconstructed from responses to all 984 tone presentations. Briefly, a summed peri-stimulus time histogram (PSTH) was generated from responses to all 984 tone pips (41 frequencies x 8 intensities x 3 repeats). The spontaneous firing rate of the multiunit was taken as the mean firing rate in the 50-ms window prior to stimulus onset. Peak latency was defined as the time to the peak PSTH response between 7 and 50 ms after the stimulus onset. The response window was defined as the continuous period encompassing the PSTH peak, in which the mean firing rate in every bin was higher than the baseline spontaneous firing rate. The onset latency was defined at

the onset of the response window, and the offset latency was defined at the end of the response window. Spikes that occurred within the response window were counted to reconstruct the receptive field.

The tuning curve contour was determined using a smoothing and thresholding algorithm (for details and to see the effects of smoothing and thresholding, please see Figure 2 of Yang et al., 2014). Briefly, the response magnitude was plotted in the frequency-intensity space, filtered with a 3x3 mean filter, and thresholded at 35% of the maximum of the filtered response magnitude. Response areas smaller than 5 pixels were considered noise and removed. The contour of the suprathreshold area was used as the tuning curve. The raw responses in the suprathreshold area was considered to be the isolated receptive field. The threshold of the neuron was defined as the lowest sound level that elicited responses in the isolated receptive field. The characteristic frequency (CF) of a neuron was defined as the center of mass of the isolated receptive field (RF) for the two lowest suprathreshold sound levels. The maximum RF response was the maximum number of spikes activated by a single frequency-intensity combination. The mean and median RF response were the mean or median, respectively, number of spikes for all frequency-intensity combinations within the receptive field. Tuning bandwidth (BW) was defined as the bandwidth (on the logarithmic scale, in octaves) of the receptive field at the specified intensity. We quantified BW at 80, 70 and 60 dB, but not at lower SPLs (< 60 dB) because many neurons did not respond at those low levels. To accurately quantify BW at low SPLs, we also measured BW at 10, 20 and 30 dB above the threshold. The receptive field size was the number of frequency-intensity combinations within the receptive field.

AI space was tessellated (with the voronoi function in MATLAB) into polygons, and

each polygon was assigned the response properties of the corresponding recording site to generate auditory cortical maps.

Statistics. Unless otherwise stated in the text, statistical significance was determined with ANOVAs with post hoc Bonferroni's test. All response properties were averaged for each animal and compared between groups. Results were presented as mean ± SEM.

RESULTS

The cortical frequency map in AI was examined in blast- and sham-exposed animals 3 months after the exposure. AI frequency maps of sham-exposed animals were tonotopically organized, with all frequencies approximately equally represented in each animal (one-sample Kolmogorov-Smirnov test against a log-uniform distribution from 2 kHz to 32 kHz, $p > 0.1$; for example, see **Figure 1**, Z-3 and Z-14). By contrast, all blast-exposed animals had a large area in AI that over-represented a relatively narrow frequency band (Kolmogorov-Smirnov test, $p < 0.001$; **Figure 1**). Two animals had over-representations of low frequencies (e.g., Z-12 in **Figure 1**), two over-represented middle frequencies (e.g., Z-7 in **Figure 1**) and one over-represented high frequencies (Z-5 in **Figure 1**).

Inspection of receptive fields (**Figure 2**) suggests substantial differences in neuronal response properties, such as tuning bandwidth and sound threshold. Quantitative analysis indicates that AI neurons in the blast-exposed animals had higher thresholds than those of the sham-exposed animals (one-way ANOVA, $F_{1,8} = 5.97$, $p = 0.040$; **Figure 3**). This is consistent with a high ABR threshold in the blast- compared to the sham-exposed animals (Luo et al., 2014b).

We plotted threshold maps (**Figure 4**) to illustrate the topographic organization of the neuronal response threshold. While blast-exposed animals had higher thresholds in general compared to the sham-exposed group (see **Figure 3**), the range of frequencies with higher thresholds within a map appeared to be variable for the blast-exposed animals. Furthermore, neuronal response threshold changes do not appear to be correlated with expansions of frequency representation. For example, Z-7 and Z-12 had higher thresholds in the expanded frequency ranges compared to other frequency ranges (i.e., fewer blue sites; see **Figure 4**), whereas Z-5 had lower thresholds in the expanded frequency range relative to other frequency ranges (more blue sites; the expanded frequency ranges in the blast-exposed animals are shown in **Figure 1**).

We measured two types of tuning bandwidths—tuning bandwidth at specified sound levels, and tuning bandwidth at intensities relative to the intensity threshold. The results indicate that bandwidth was significantly broadened at 50 and 60 dB SPL (**Figure 5**; Group x Sound-level two-way ANOVA; Group effect, $F_{1,24} = 15.01$, $p < 0.001$; Sound level effect, $F_{2,24} = 10.21$, $p < 0.001$; Post Hoc test, $p < 0.05$ at 50 and 60 dB SPL), and at 20 and 30 dB above the intensity threshold for AI neurons in the blast-exposed animals compared to sham-exposed animals (Group x Sound-level two-way ANOVA; Group effect, $F_{1,24} = 13.11$, $p = 0.0014$; Sound level effect, $F_{2,24} = 24.64$, $p < 0.001$; Post Hoc test, $p < 0.05$ at 20 and 30 dB above threshold). In addition, the onset, peak, and offset latency of the cortical responses to tonal stimulus are significantly shorter in the blast-exposed animals compared to controls (**Figure 6**; Mann-Whitney test $n_1 = n_2 = 5$: onset, $U = 2.50$, $p = 0.035$; peak, $U = 1.00$, $p = 0.016$; offset $U = 0.001$, $p = 0.009$).

We measured spontaneous activity as the mean number of spikes in the 50-ms window right before the onset of the tonal stimulus, and found no difference between the control and the blast-exposed groups (**Figure 7**, ANOVA, $F_{1,8} = 0.065$, $p = 0.81$). We also measured median, mean and maximum responses of cortical neurons to tones in the frequency-intensity response area. There were no differences in either of these measures between the blast-exposed and the control groups (**Figure 7**, ANOVA, $p > 0.5$ for all measures).

DISCUSSION

In this study we have shown that blast exposure disrupts the AI frequency map and changes neuronal response properties. Some of these changes are similar to those observed in animals following noise exposure. For example, the increased response threshold and shortened response latencies observed in this study have previously been reported following noise exposure (Gallo and Glorig, 1964; Syka and Rybalko, 2000; Norena et al., 2003). Noise exposure often results in hearing loss in a limited frequency range, causing a shift of neuronal tuning away from the hearing loss frequencies and towards the neighboring frequencies. The consequent map reorganization typically manifests as expanded representation of the frequencies flanking the hearing loss frequency range (Yang et al., 2011).

The blast exposure procedure used in this study has been previously shown to cause TBI (Mao et al., 2012). TBI typically elevates the expression of pro-inflammatory cytokines in the brain (Bermpohl et al., 2007), which in turn modulate neuronal functions such as synaptic transmission and membrane excitability. For example, TBI often increases TNF-α expression (Bermpohl et al.,

2007), and TNF-α increases the excitation-to-inhibition ratio by enhancing excitatory synapses and weakening inhibitory synapses (Beattie et al., 2002; Stellwagen and Malenka, 2006). This process could lead to amplification of small differences in the level of (possibly hidden) hearing loss across different frequencies, resulting in disproportional AI map reorganization.

One observation in the present study that deviated from previous reports (Luo et al., 2017) is the lack of changes in AI neural activity and responses (**Figure 7**). Noise and blast exposure have previously been shown to increase spontaneous and sound-evoked activity in the auditory cortex (Eggermont and Roberts, 2004; Kotak et al., 2005; Luo et al., 2017). However, we did not observe those types of changes. This may be due to the differences in experimental preparation and recording conditions. We recorded cortical multiunit activity in acute preparation, from anesthetized animals, and we compared activity between different animals. A better way to compare neural activity is through chronic recording of single unit activity in awake animals before and after blast exposure. It is also possible that changes in AI neural activity occur in a specific time window following blast exposure, and that our experiment took place after the activity had recovered. This could also be addressed by using chronic recording of neuronal activity to track activity changes. A third possibility is that blast-induced TBI and hearing loss have opposite effects on neuronal activity. If so, we may observe an increase, no change, or a decrease in spontaneous and evoked activity depending on the type and degree of TBI and/or hearing loss.

Blasts cause hearing loss and TBI, both of which are related to tinnitus. Hearing loss is the largest risk factor for tinnitus (Nondahl et al., 2002; Nelson and Chen, 2004). It disrupts

excitation-inhibition balance, and increases spontaneous, synchronous, and/or burst firing in the central auditory pathway (Seki and Eggermont, 2003; Kotak et al., 2005; Eggermont, 2007). These changes in central auditory activity have been considered potential mechanisms underlying tinnitus (Eggermont and Roberts, 2004). Traumatic brain injury (TBI), such as what results from blast exposure, is also a significant risk factor for tinnitus (Vernon and Press, 1994; Folmer and Griest, 2003; Lew and Guillory, 2007). For example, the incidence of tinnitus is higher in military personnel with TBI compared to those without TBI, with up to 38% of veterans suffering from TBI also experiencing tinnitus (Lew and Guillory, 2007). TBI-triggered increases in the pro-inflammatory cytokine TNF-α may increase the excitation-to-inhibition ratio (Beattie et al., 2002; Stellwagen and Malenka, 2006) and increase the incidence of tinnitus. Sensory map reorganization has been proposed as a potential mechanism underlying tinnitus (Eggermont, 2006; Engineer et al., 2011). Such a notion seems to be supported by our observation that AI frequency mapping was disrupted by blast exposure. Blasts may cause central auditory processing disorder in the absence of hearing threshold increases, such as difficulty listening in noisy environment (Saunders et al., 2015; Bressler et al., 2017). Disrupted auditory frequency maps may contribute to this pathological condition. Further studies are needed to determine a causal relationship between the two blast-caused pathologies.

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FIGURES

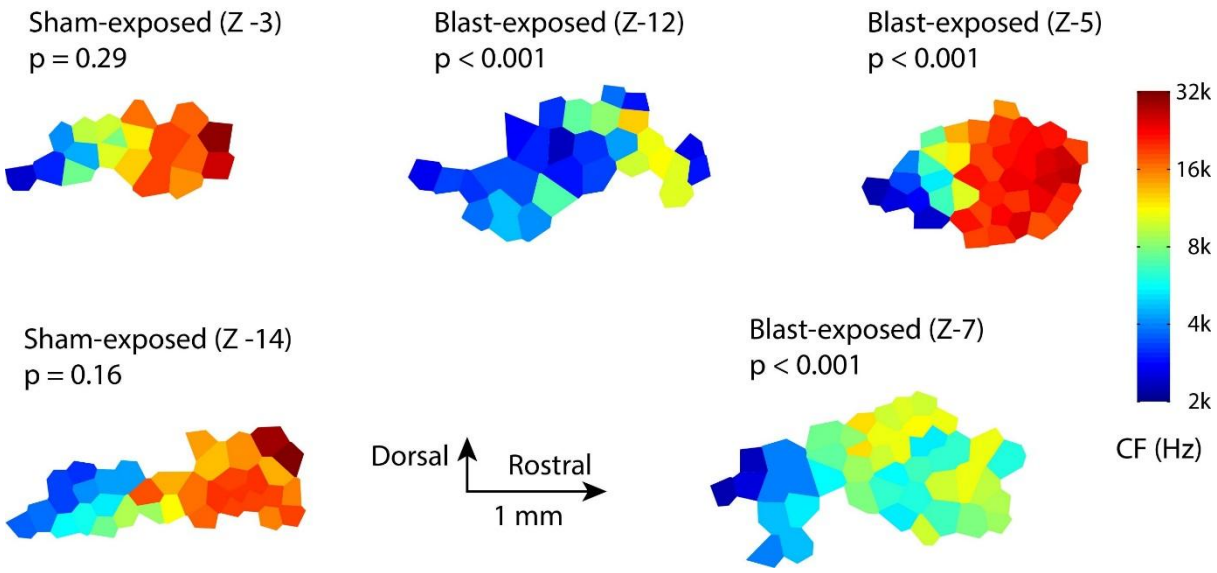

Figure 1. Representative cortical frequency maps showing disrupted cortical map in blast-exposed animals. Control maps (Z-3 and Z-14) showed tonotopic representation of the complete frequency spectrum from 2-4 kHz to 32 kHz. By contrast, maps from blast-exposed animals showed disproportionally large representations of seemingly random and narrower frequency ranges. For example, Z-12 had enlarged representations of low frequencies (blue colors), Z-7 had enlarged representations of middle frequencies (blue and yellow colors) and Z-5 had enlarged representation of high frequencies (red colors). The p values are presented for one-sample Kolmogorov-Smirnov tests against a log-uniform distribution from 2 kHz to 32 kHz.

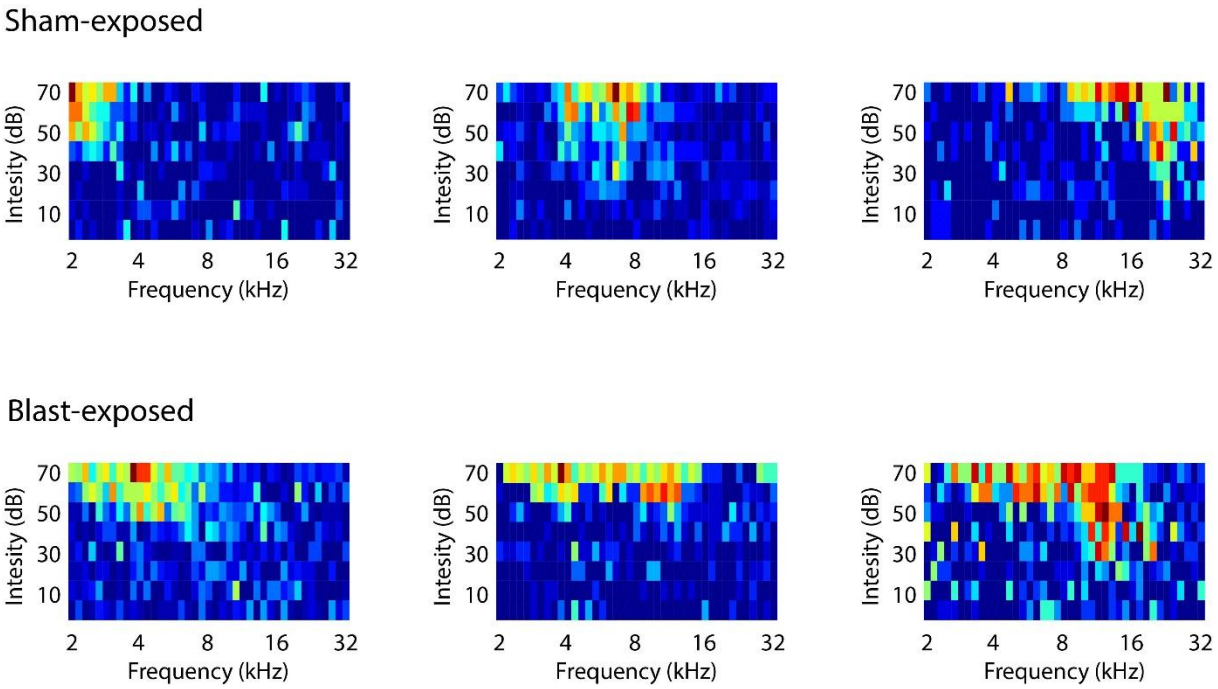

Figure 2. Representative receptive fields from control and blast-exposed animals. Receptive field from blasted animals are generally more broadly tuned, and with a higher threshold. Horizontal axis depicts frequency from 2 to 32 kHz with 0.1 octaves steps. Vertical axis depict intensity from 0 to 70 dB SPL with 10 dB steps.

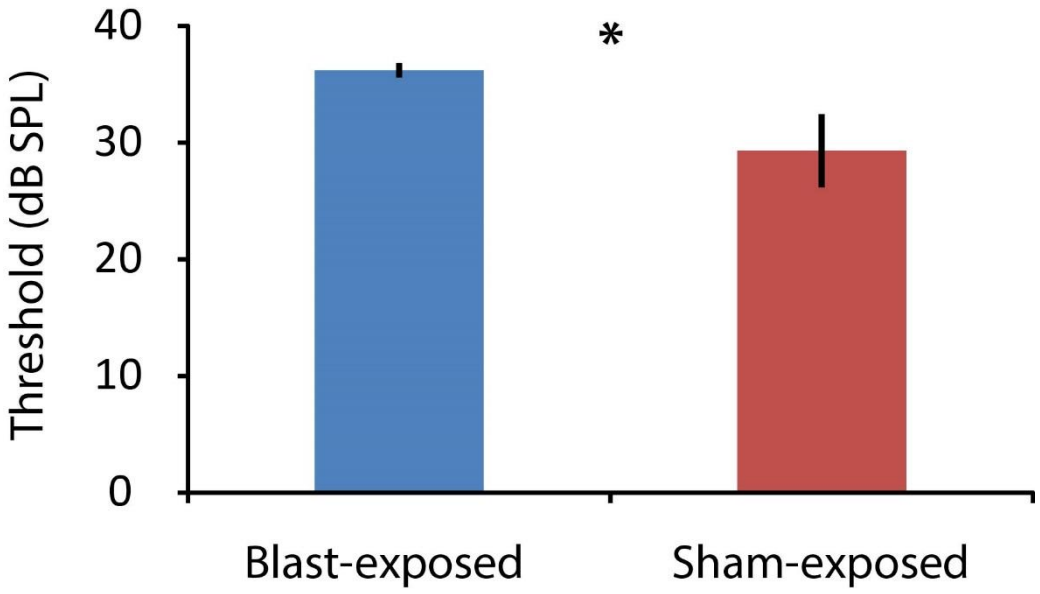

Figure 3. Intensity threshold was elevated for blast-exposed animals. Error bars represent SEM and * indicates $p < 0.05$.

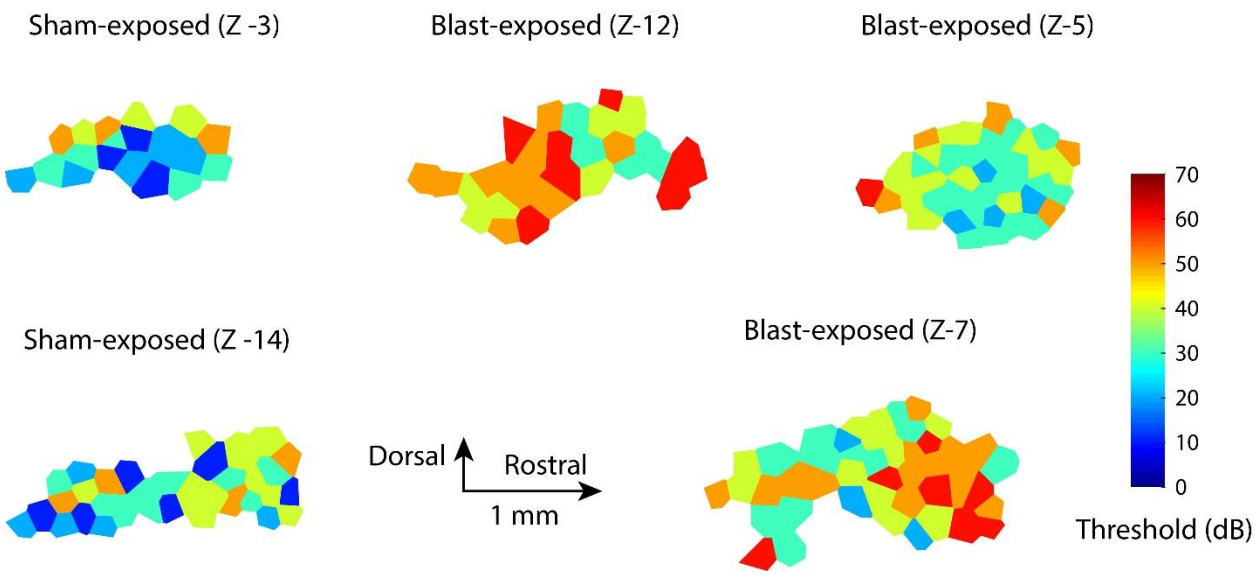

Figure 4. Representative cortical threshold maps showing elevated sound threshold in blast-exposed animals. Control maps (Z-3 and Z-14) showed low response thresholds at most of the recorded sites. By contrast, maps from blast-exposed animals showed middle and high thresholds at most of the recorded sites. These maps were from the same animals as those in Figure 1.

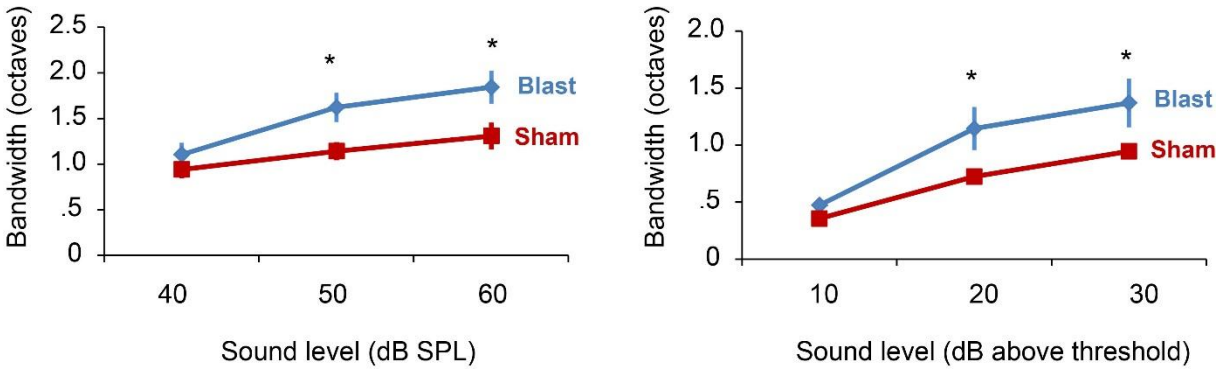

Figure 5. Cortical tuning bandwidths were elevated in blast-exposed animals. Blue: blast-exposed group (n = 5); red: control group (n = 5). Error bars represent SEM. * indicates $p < 0.05$.

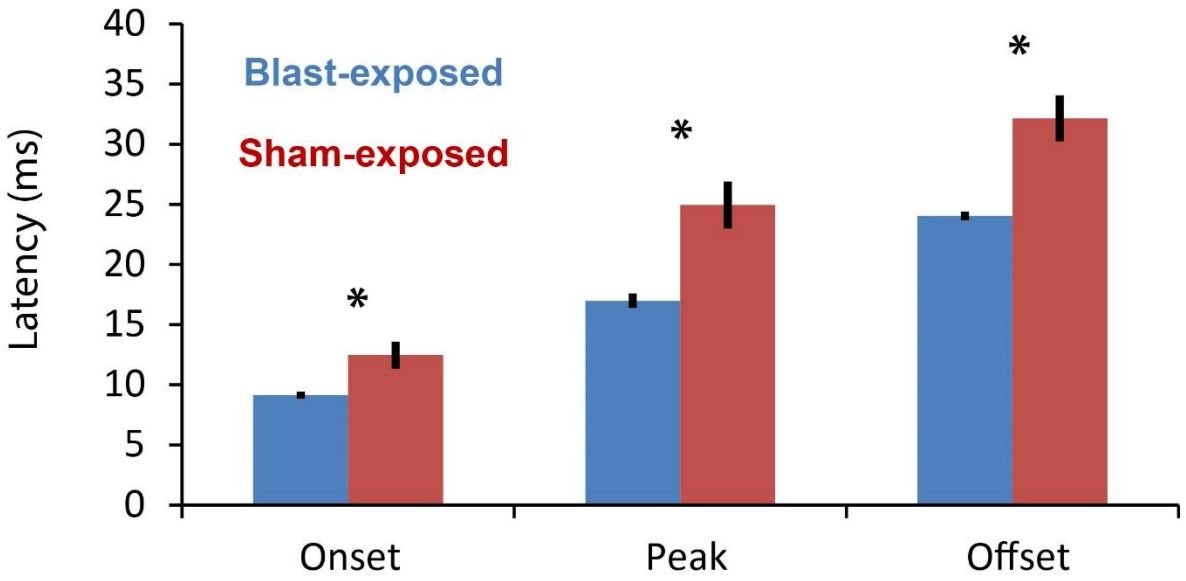

Figure 6. Onset, peak and offset latencies of the cortical responses were significantly reduced in blast-exposed animals. Blue: blast-exposed group (n = 5) ; red: control group (n = 5). Error bars represent SEM. * indicates $p < 0.05$.

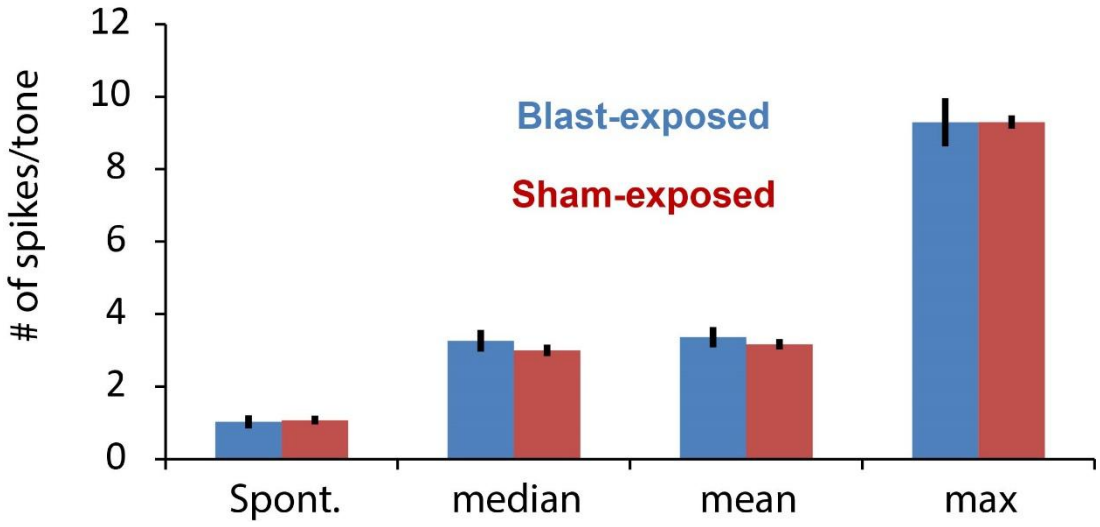

Figure 7. There were no differences in spontaneous activity, or median, mean or maximum response to tones between the control and the blast-exposed groups. Blue: blast-exposed group; red: control group. The two groups were not significantly different in any of the measures. Error bars represent SEM.

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