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Behavioral and Neural Discrimination of Speech Sounds After Moderate or Intense Noise Exposure in Rats

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Abstract

Objectives—Hearing loss is a commonly experienced disability in a variety of populations including veterans and the elderly and can often cause significant impairment in the ability to understand spoken language. In this study, we tested the hypothesis that neural and behavioral responses to speech will be differentially impaired in an animal model after two forms of hearing loss.

Design—Sixteen female Sprague–Dawley rats were exposed to one of two types of broadband noise which was either moderate or intense. In nine of these rats, auditory cortex recordings were taken 4 weeks after noise exposure (NE). The other seven were pretrained on a speech sound discrimination task prior to NE and were then tested on the same task after hearing loss.

Results—Following intense NE, rats had few neural responses to speech stimuli. These rats were able to detect speech sounds but were no longer able to discriminate between speech sounds. Following moderate NE, rats had reorganized cortical maps and altered neural responses to speech stimuli but were still able to accurately discriminate between similar speech sounds during behavioral testing.

Conclusions—These results suggest that rats are able to adjust to the neural changes after moderate NE and discriminate speech sounds, but they are not able to recover behavioral abilities after intense NE. Animal models could help clarify the adaptive and pathological neural changes that contribute to speech processing in hearing-impaired populations and could be used to test potential behavioral and pharmacological therapies.

Keywords

Cortical plasticity; Hearing loss; Noise exposure; Rat; Speech discrimination

INTRODUCTION

Animal models of speech processing have provided valuable information about the neural basis of speech sound discrimination. Animals can be readily taught to discriminate speech sounds (Kuhl & Miller 1975; Kluender et al. 1987; Reed et al. 2003; Engineer et al. 2008). The discrimination abilities of rats and other mammals mirror those of humans, in that behavioral tasks that humans find difficult are also difficult for animals to perform (Engineer et al. 2008; Perez et al. 2013). Rats can easily discriminate sounds in a quiet background, but have more difficulty when sounds are presented in a noisy background (Shetake et al. 2011). Behavioral accuracy of rats is also similar to humans in discrimination tasks using consonant and vowel sounds that have been spectrally and temporally degraded (Ranasinghe et al. 2012b).

One of the greatest advantages of animal models of speech discrimination is that detailed neural responses to the same speech sounds can be recorded and compared to behavioral responses. Multiunit intracortical recordings provide more detail about the spatial and temporal patterns of brain activation caused by speech stimuli than can be recorded in healthy human subjects. Speech sounds and other complex stimuli produce complicated spatial and temporal patterns of activation throughout the auditory system. Previous studies have found that these patterns of activation can accurately predict the discrimination abilities of animals (Engineer et al. 2008; Perez et al. 2013; Centanni et al. 2014). Impaired speech discrimination caused by embedding sounds in noise or filtering out temporal and spectral information can be explained by analysis of the corresponding degradation of responses in primary auditory cortex (A1) (Shetake et al. 2011; Ranasinghe et al. 2012b). Speech discrimination can be impaired by damage to the auditory cortex in rats (Porter et al. 2011), which confirms the importance of this brain region in speech sound processing.

In humans, the most common cause of speech perception impairment is peripheral hearing loss (Plomp 1978; Boothroyd 1984; Helfer & Wilber 1990; Blamey et al. 2001; Lorenzi et al. 2006). No study to date has documented both behavioral and neural discrimination of speech sounds after intense noise exposure (NE). Intense NE causes damage to the cochlea and leads to plasticity and reorganization of the auditory system in rats. Many previous studies have examined how NE changes the basic response properties of the auditory system in rats, such as tonotopic organization, receptive field sizes, and responses latencies (Eggermont & Komiyama 2000; Seki & Eggermont 2002, 2003; Norena et al. 2003; Norena & Eggermont 2005, 2006; Engineer et al. 2011). However, these studies did not examine how this reorganization affects the neural and behavioral responses to complex stimuli such as speech.

In the present study, we exposed rats to two types of sound exposure to induce hearing loss. The two conditions, moderate NE and intense NE, varied by frequency and intensity and created two distinct types of noise trauma, both of which have been encountered in clinical populations (Axelsson & Sandh 1985; Moscicki et al. 1985). Neural responses to both tones and speech were recorded from the auditory cortex of noise-exposed animals and compared to controls. We found that both types of NE led to long-term changes in the patterns of activity evoked by speech sounds in the primary auditory cortex. In addition, we tested

operant discrimination of speech sounds in rats with each type of hearing loss and found that intense NE dramatically affected behavioral performance while moderate NE had no lasting effects.

EXPERIMENTAL PROCEDURES

A total of 26 female Sprague–Dawley rats (aged 2–6 months, weighing 275–350 g) were used for this study (see Table 1 for sample size by group). Of these, six were controls, which did not receive any NE or behavioral training and were used for neural recordings only. Sixteen rats were exposed to one of two noise conditions. In nine of these rats ($N = 5$ exposed to moderate noise and $N = 4$ exposed to intense noise), physiological recordings were taken 4 weeks after NE to quantify how NE affected neural responses to speech and to tones. The remaining seven rats ($N = 4$ in the moderate noise group, $N = 3$ in the intense noise group) were pretrained to perform an operant speech discrimination task before NE. The speech-trained rats performed an additional two weeks of speech discrimination testing beginning four weeks after NE. All protocols and recording procedures were approved by the University of Texas at Dallas Institutional Animal Care and Use Committee (Protocol Number: 99-06).

NOISE EXPOSURE

Two NE protocols were used to produce hearing loss. For the moderate NE group, all rats were exposed to one-octave broadband noise centered at 16 kHz at 115 dB SPL. Previous studies have shown that this exposure causes severe hearing loss for several days with some long lasting changes in tone thresholds, especially in sites tuned to high-frequency tones (Syka & Rybalko 2000; Bauer 2003; Turner et al. 2006; Wang et al. 2009; Engineer et al. 2011; Browne et al. 2012). For the intense NE group, the rats were exposed to one-octave broadband noise centered at 4 kHz at 125 dB SPL. The parameters of this noise were chosen to ensure that this sound would cause permanent damage to the rat's hearing in both the low- and high-frequency range (Yamasoba et al. 1999; Yang et al. 2011). Auditory thresholds differ by the frequency of the tone, such that 16 kHz has a lower threshold than 4 kHz (Kilgard & Merzenich 1999). The higher intensity level used to induce permanent hearing loss was designed to compensate for this baseline difference in auditory thresholds. All rats were noise-exposed for 1 hr while anesthetized with ketamine hydrochloride (80 mg/kg) and xylazine (10 mg/kg). Anesthesia was used during NE to prevent movement relative to the speaker and to allow for comparison with earlier studies using this procedure (Engineer et al. 2011). We waited 4 weeks after NE to allow changes in neural response properties to stabilize before we assessed how the neural and behavioral responses to speech were altered (Turner et al. 2006; Engineer et al. 2011; Yang et al. 2011). A single free-field speaker (Optimus) was located 5 cm from the left ear (i.e., contralateral to the neural recording sites), but both ears were unoccluded during NE. Sound intensity calibrations were performed using an ACO Pacific microphone (PS9 200–7016) and custom-written MATLAB software.

Neural Recordings

The methods for neurophysiological recordings have been described in previous publications (Engineer et al. 2008, 2011; Reed et al. 2011). Briefly, rats were anesthetized using pentobarbital anesthesia (50 mg/kg). A tracheostomy was performed to improve breathing and reduce breathing noise. A cisternal drain was inserted to prevent cranial swelling. The right temporal bone was removed and the dura resected to expose the right auditory cortex. Silicone oil and saline were placed in the craniotomy to prevent desiccation of the auditory cortex. Neurophysiological recordings were taken using bipolar platinum–iridium electrodes (250 μ m separation, 1–2 MOhm at 1 kHz; FHC Inc., Bowdoinham, ME). Multiunit recordings were taken from layer IV of the cortex (depth $\sim$ 600 μ m). The number of individual neurons contributing to each multiunit cluster in this study is unknown. Layer IV is an input layer and a common target for auditory recording studies (Polley et al. 2007; Engineer et al. 2008, 2013; Centanni et al. 2013a). Sounds were presented from a speaker (Tucker-Davis Technologies, ES1) placed 10 cm away from the animal's left ear. Recordings were amplified, filtered, and digitized using Tucker-Davis equipment, as in our previous studies (Engineer et al. 2008, 2011, 2013, 2014a, b; Reed et al. 2011; Shetake et al. 2011; Ranasinghe et al. 2012a, b; Centanni et al. 2013a, b, 2014; Perez et al. 2013). A tuning curve was measured at each site to determine characteristic frequency. The stimuli consisted of 25 ms duration tones played at intensities ranging from 0 to 75 dB and frequencies ranging from 1 to 47 kHz.

The receptive field properties of each site were automatically calculated using custom software. The spontaneous firing rate of each site was calculated as the average response rate over the first 8 ms after each tone presentation (i.e. before stimulus-driven responses were possible). The minimum latency of each site was calculated as the first time point after sound presentation when the firing rate for a site was more than two standard deviations above the spontaneous firing rate for four consecutive milliseconds. The end of peak latency was calculated as the first time point in which the firing rate fell to less than two standard deviations above the spontaneous firing rate for two consecutive milliseconds. The peak latency was the time of maximum firing between the minimum and end of peak latency. The receptive field was defined as the continuous range of frequencies and intensities that reliably evoked driven activity. The threshold was calculated as the minimum intensity that still evoked a driven response. The characteristic frequency was the frequency at which the threshold response was evoked. Bandwidths (BW) were calculated as the range of driven activity at 10–40 dB above the threshold (BW 10–40). The driven rate was calculated as the average firing rate evoked by all tones within the receptive field. As in earlier studies, Voronoi tessellation was used to transform the discretely sampled surface into a continuous map using the assumption that each point on the map has the response characteristics of the nearest recording site (Kilgard & Merzenich 1998; Engineer et al. 2011; Reed et al. 2011). Since regions with above-average sampling density have smaller tessellations, they do not bias estimates of the cortical response. A1 sites were identified on the basis of short onset latency (less than 20 ms from stimulus onset), sharp tuning, and topography such that characteristic frequencies were arranged low to high in a posterior to anterior direction (Centanni et al. 2013a). In the case of the intense NE group, all sites that responded to tones were identified as A1 sites regardless of latency or topography. Because of the low number

of responsive sites found in pilot testing, we analyzed the maps of previous control animals and identified the cortical area which most often contained A1. For this study, we mapped intense NE rats using this grid as a guide. Any site that was found to respond within this “known A1” area was classified as A1 for the purpose of this study. The percent of the cortical area of A1 responding to each tone was estimated as the sum of the areas of all tessellations from sites in A1 with receptive fields that included the tone, divided by the total area of A1.

For each experiment, we recorded from approximately 60 sites. We sampled from many sites in the intense NE group that were not responsive to tones because we wanted to thoroughly explore the regions of cortex where A1 responses would normally be found. To systematically search this region, we compiled data from over 20 previously completed naïve control A1 maps and determined where within the craniotomy A1 and auditory responses were usually found. These control animals were of the same ages and weights as the animals used in this study and had heard the same tuning curve stimulus set but were mapped during previous studies (Reed et al. 2011). We then made sure to sample this area at a minimum density of 1 penetration per 0.15 mm² during recordings. When we found a region of cortex that was still responsive to tones, this region was sampled as densely as possible. The average sampled area was slightly higher in the intense NE group (3.94 ± 0.58 mm²) compared to either the moderate NE group (2.80 ± 0.63 mm²) or the control group (2.99 ± 0.18 mm²), but there were no statistically significant differences between any group in the area of auditory cortex that was sampled.

The following speech sounds were played during each penetration: “dad,” “bad,” “chad,” “gad,” “sad,” “shad,” “tad,” “dead,” “deed,” “dood,” “dud.” The sounds “dead,” “deed,” “dood,” and “dud” were compared to the sound “dad” for a comparison in how changing vowels changed neural responses, while the remaining speech sounds were used for consonant comparisons. Each speech sound was recorded by a female native English speaker in a soundproof booth. As in our earlier studies (Engineer et al. 2008, 2013, 2014a, b; Porter et al. 2011; Shetake et al. 2011; Ranasinghe et al. 2012a, b; Centanni et al. 2013a, b, 2014; Perez et al. 2013), the sounds were shifted upwards 1 octave to better match the rat's hearing range using the STRAIGHT vocoder (Kawahara 1997). Each sound was calibrated in both the physiology and behavioral booths so that the loudest 100 ms of the sound was 60 dB SPL using an ACO Pacific microphone (PS9 200–7016) and custom written MATLAB software. The onset latency for each speech sound response was calculated by finding the first time point in which the strength of response of the average poststimulus time histogram for all control sites reached three standard deviations above the average spontaneous firing rate. For all sites in all groups, the peak latency was calculated as the time from the onset latency observed in controls to the maximum firing rate of each site. During analysis, we only included sites that had a peak firing rate of at least 0.05 spikes/ms to at least one of the speech sounds in our analysis. This criteria did not eliminate any A1 sites (out of 207) from the control group, but it eliminated 3 (out of 124) A1 sites from the moderate NE group and 17 (out of 59) A1 sites from the intense NE group. For consonants, the driven firing rate was calculated as average firing rate in the first 75 ms after the onset latency for each speech sound (this larger window was to account for the very slow responses of some sites in the intense NE group; sites in the moderate NE and control

groups generally responded within 40 ms). For vowels, the driven firing rate was calculated as the average firing rate from 50 to 350 ms after the onset.

We used a Euclidean distance formula to calculate the similarity of neural responses to different consonant speech sounds, as in our previous studies (Engineer et al. 2008; Centanni et al. 2013a, b; Perez et al. 2013). The Euclidean distance between any two sets of neural responses is the square root of the sum of the squared differences between the firing rate at each bin (j). We used the activity from forty 1-ms bins from all A1 to compute the similarity between the sound “dad” and every other speech sound. The following formula was used:

$$\text{Euclidean Distance} = \sqrt{\sum_{j=1}^{\#bins} (x_j - y_j)^2}$$

where # bins is the total number of bins. The neural similarity values reported are the average Euclidean distance across individual A1 sites.

Behavior Training

Seven rats were trained to perform a go/no-go speech discrimination task, which has been described in previous publications (Engineer et al. 2008, 2014b; Porter et al. 2011; Shetake et al. 2011; Ranasinghe et al. 2012b; Perez et al. 2013). Animals were required to press a lever after they heard the sound “dad” and refrain from hitting when any of the several distracters were presented. In this study, the distracters differed either in the initial consonant (“tad,” “bad,” “gad”) or the vowel (“dud,” “deed,” “dood”). This same task has been used in previous studies (Engineer et al. 2008, 2014a, b; Porter et al. 2011; Ranasinghe et al. 2012b).

All animals were food deprived and maintained at 85–90% of their ad libitum body weight. Food rewards consisted of a 45 mg pellet (Bio-Serv). The rats were placed in a 20 cm by 20 cm cage in a soundproof booth. Animals pressed a lever to respond to sounds and received their rewards from a pellet receptacle located next to the lever. A speaker (Tucker-Davis Technologies, ES1) located ~20 cm away from the rats left ear (when the rat was sitting between the pellet receptacle and lever) delivered sounds. A house light located above the cage provided illumination and was extinguished during “time-outs” after animals made an incorrect lever press.

Animals received a food pellet when they pressed the lever within 3 sec after hearing the word “dad” and received a 6-sec time-out when they pressed after a distracter or during silent intervals (all the cage lights were extinguished and sound presentations were delayed). Approximately 46% of trials contained a target, 46% contained a distracter, and 8% contained silent catch trials. We collected two weeks of speech discrimination data to form a baseline and then exposed the rats to noise. Four rats were exposed to the 16 kHz noise (moderate NE) and three rats were exposed to the 4 kHz noise (intense NE). The rats were allowed to recover for 4 weeks and then retested on the speech discrimination task for an additional 2 weeks.

To evaluate behavioral performance, we used the signal detection theory measure d' (Green & Swets 1966; Klein 2001). The d' measure compares the responses to the target and distracter sounds. A d' value of 0 indicates that the rat cannot discriminate between the target and distracter sounds, while a more positive d' value ($d' \geq 1.5$) indicates successful discrimination of the sounds. We also examined the raw percent of trials in which animals pressed the lever in response to a target, distracter, or a silent catch trial. Lever presses within 3 sec of the beginning of each trial type (i.e. during the reward period for target stimuli) were considered during analysis.

Data Analysis

We report the results of post hoc Student's t tests comparing each experimental group (moderate or intense NE) to naïve controls. ANOVA comparisons including all three experimental groups were always statistically significant because the intense NE group was so radically different from the naïve controls on all measures. Error estimates are given in standard error of the mean.

RESULTS

This study evaluated the consequences of two different types of NE on cortical representations of speech sounds. Auditory brainstem responses (ABRs) were used to confirm that ABR thresholds were more elevated in the intense NE group compared to the moderate NE group (Fig. 1).

Receptive Field Properties

We examined receptive field properties in five rats exposed to a moderate noise (16 kHz-centered octave band noise at 115 dB SPL) for an hour (moderate NE group; see Fig. 2B for a representative site's response to tones) and in four rats exposed to an intense noise (4 kHz-centered octave band noise at 125 dB SPL) for an hour (intense NE group; see Fig. 2C for a representative site's response to tones). These two NE protocols were chosen to produce either severe hearing loss (intense NE group) or more moderate damage to the auditory system (moderate NE group). The data from these rats were compared to data collected from six naïve controls (see Fig. 2A for a representative site's response to tones).

In the intense NE group, hearing loss was so severe that there was a substantial decrease in the number of sites that were auditory responsive. Although we sampled a large area of the auditory cortex, we found that only small patches of the auditory cortex were still responsive to tones (Fig. 3C). Over two-thirds ($73.91 \pm 9.57\%$) of the sites recorded in the intense NE group were classified as being nonresponsive, compared to only $11.53 \pm 7.0\%$ in naïve controls ($p = 3.09 \times 10^{-4}$). The small patches with residual auditory responses had severely altered receptive fields (Figs. 4A, B). The average threshold in the intense NE group was 55.41 ± 0.82 dB SPL compared to 11.12 ± 0.70 dB SPL in controls (two-tailed t -test, $p = 1.82 \times 10^{-9}$; Figs. 4B, 5C). Because thresholds were so high, the intense NE group only had neural responses to tones between 4 and 16 kHz when they were presented at 60 dB SPL (the control group responded to all tones between 1 and 32 kHz, Fig. 4A). Receptive fields were significantly more narrow (BW $30:1.49 \pm 0.10$ octaves in intense NE group, $2.35 \pm$

0.06 octaves in controls, $p = 2.25\text{e-}9$, two-tailed t -test), and the responses to tones within the receptive field were much weaker than in naïve controls (driven spikes per tone: 2.25 ± 0.14 in intense NE group, 2.78 ± 0.07 in controls, $p = 6.6\text{e-}9$; Figs. 4C, 5B). It is possible that the reduced bandwidth is an artifact caused by the greatly altered thresholds and frequency distribution in the intense NE group. Neural responses were also slower (minimum latency: 12.08 ± 0.12 ms for controls and 25.0 ± 1.38 ms for intense NE, $p = 1.20\text{e-}52$; peak latency: 18.83 ± 0.20 ms for controls and 30.95 ± 1.55 ms for intense NE, $p = 4.07\text{e-}37$; Figs. 4C, 5A). These results confirm that the intense NE group had severely altered neural responses to tones one month after NE.

We also observed changes in neural responses to tones in the moderate NE group. There was no difference in the percentage of sites that were able to respond to tones or in the percentage of sites that were classified as belonging in A1 (an average of 45.83 ± 7.58 sites in control A1 vs. an average of 43.2 ± 3.65 sites in A1 after moderate NE, $p = 0.79$, two-tailed t -test, Table 2). As expected, we found that exposure to the high-frequency (16 kHz) noise band caused more changes in response properties for high-frequency tuned neurons than for low-frequency tuned neurons. After NE, the moderate NE group had low-frequency map expansions (Figs. 3B, 4A). While approximately $30.15 \pm 6.04\%$ of A1 sites in controls responded to a 1.3 kHz, 60 dB SPL tone, $63.69 \pm 8.05\%$ of sites in the moderate NE group responded to the same tone ($p = 0.047$, two-tailed t -test; Fig. 4A). This increase in the cortical response to low-frequency tones was accompanied by a decrease in the cortical response to mid-frequency tones (percent of sites responding to 6 kHz, 60 dB SPL tone; $70.62 \pm 4.56\%$ in controls; $54.33 \pm 6.11\%$ in moderate NE; $p = 0.04$, two-tailed t -test; Fig. 4A). Consistent with our previous findings of map plasticity after hearing loss, there was no change in the cortical response to high-frequency tuned sites (Fig. 4A; Engineer et al. 2011). When we examined the receptive field properties of individual sites, we found that the moderate NE group had elevated thresholds, but only for high-frequency sites (i.e., sites tuned to frequencies above 5.6 kHz) (Threshold for high-frequency tuned sites; 13.61 ± 1.05 dB SPL for controls; 22.01 ± 2.10 dB SPL for moderate NE; $p = 0.0001$; two-tailed t -test; Fig. 4B). The driven response rate of sites tuned to high frequencies after NE was significantly lower than in controls (driven response for high-frequency sites; 2.72 ± 0.09 spikes/tone in control vs. 2.21 ± 0.10 spikes/tone in moderate NE; $p = 0.0002$, two-tailed t -test), but the driven response rate of low-frequency tuned sites after NE was not significantly different (driven response for low-frequency sites; 2.87 ± 0.10 spikes/tone for controls; 2.75 ± 0.09 spikes/tone for moderate NE; $p = 0.37$; two-tailed t -test). End of peak latencies in these high-frequency sites were also significantly longer (end of peak latency; 42.54 ± 1.51 ms for controls; 55.94 ± 3.24 ms for moderate NE; $p = 3\text{e-}5$, two-tailed t -test; Fig. 4C), and spontaneous firing rates were significantly lower (spontaneous firing rate; 0.02 ± 0.001 spikes/ms for controls; 0.009 ± 0.0008 spikes/ms for moderate NE; $p = 1.57\text{e-}17$, two-tailed t -test; Fig. 4D). These results are consistent with previous studies that used similar NE and indicate that although the moderate NE group had robust responses to tones, latency and receptive fields were significantly altered (Norena et al. 2003; Seki & Eggermont 2003; Norena & Eggermont 2005; Aizawa & Eggermont 2006; Engineer et al. 2011). We predicted that these changes would also affect how neurons in A1 responded to speech.

Neural Responses to Speech

We collected neural responses to speech sounds in four of the six control animals used for tone response data collection. These animals had not been trained on the speech discrimination task. Our analysis of consonants focused on the onset response because previous studies from our lab demonstrated that differences in the spatiotemporal activity patterns within 40 ms of speech onset were well correlated with consonant discrimination ability (Engineer et al. 2008; Ranasinghe et al. 2012b; Centanni et al. 2013a, 2014). In normal-hearing controls, each individual speech sound produced a unique pattern of activity in A1, as has been consistently replicated in a variety of species (Steinschneider et al. 1994, 1999; Engineer et al. 2008; Centanni et al. 2013a; Perez et al. 2013). For example, the word “dad” activated neurons in both the low- and high-frequency regions of the cortex (Fig. 6A, left-hand panel and Fig. 7A). In contrast, the consonant “sad” produced only onset activity in the high-frequency region of the cortex (Fig. 6A, middle panel and Fig. 7B). For other contrasts, there was little difference in the spatial activity pattern and a clear difference in the temporal characteristics of the evoked activity. For example, “bad” produced a short latency burst of activity in low-frequency neurons and a more delayed response in high-frequency neurons (Fig. 6A, right-hand panel and Fig. 7C). The response to “dad” exhibited the opposite pattern and had an early response by high-frequency neurons and a delayed response by low-frequency neurons (Fig. 6A, left-hand panel and Fig. 7A). These spatiotemporal patterns, evoked by stop consonant stimuli, replicate our earlier findings (Engineer et al. 2008). In the present study, we extended the analysis window for consonants from 40 ms out to 75 ms because latencies were longer in both experimental groups (Figs. 6B, C).

Exposure to high-frequency noise (moderate NE group) altered the patterns of activity produced by speech sounds compared to controls. We found that speech responses in both high- and low-frequency tuned sites were altered after NE. Although low-frequency tuned neurons in the moderate NE group had relatively normal responses to tones (Figs. 4B–D), these sites did not respond normally to speech sounds. The latency of response to speech sounds was consistently later than in naïve control animals (average peak latency to all consonants in low-frequency tuned sites; 37.33 ± 1.11 ms in controls; 46.24 ± 0.72 ms in moderate NE group; $p = 6.04\text{e-}10$). For example, low-frequency sites in the moderate NE group responded ~8 ms slower to the sound “dad” than low-frequency sites in naïve controls (Fig. 8A $p = 8.69\text{e-}10$). The driven response rate of low-frequency sites in response to the consonant “dad” was unchanged after moderate NE ($p = 0.20$; Fig. 8B), and the driven response rate to all consonants was similarly unchanged (average driven response to all consonants; 0.071 ± 0.0036 spikes/ms in controls; 0.062 ± 0.0029 spikes/ms in moderate NE group; $p = 0.4813$). High-frequency tuned sites also had degraded responses to speech sounds after moderate NE. The latency of response was ~12 ms longer in response to the word “dad” in the moderate NE group compared to controls ($p = 3.75\text{e-}18$; Fig. 8A), but the driven response rate to “dad” was not significantly lower in high-frequency sites compared to naïve controls ($p = 0.24$; Fig. 8B). When all consonants were considered together, latencies were longer (average peak latency to all consonants in high-frequency tuned sites; 34.15 ± 0.77 ms in controls; 45.18 ± 1.39 ms in moderate NE; $p = 1.46\text{e-}11$) and the response strength was weaker in the moderate NE group compared to controls (average

response rate to all consonants in high-frequency tuned sites; 0.073 ± 0.0035 spikes/ms in controls; 0.044 ± 0.0049 spikes/ms in moderate NE group; $p = 5.7943\text{e-}4$). In summary, all A1 sites in the moderate NE group responded more slowly to speech sounds compared to naïve controls, but only high-frequency tuned sites had weaker responses to speech sounds.

Although moderate NE changed the pattern of speech responses compared to naïve controls, the responses in A1 were still robust, and there were still observable differences in how each individual speech sound was represented. For example, the speech sound “dad” still activated both low- and high-frequency neurons, while the speech sound “sad” only activated high-frequency sites (Figs. 6B, 7A, B). The temporal response pattern to “dad” and other consonants was preserved as well; “dad” evoked activity in high-frequency tuned neurons slightly earlier than it evoked activity in low-frequency tuned neurons (Figs. 6B, 7A). The patterns of activity produced by “bad” in both low- and high-frequency tuned neurons were readily distinguished from the pattern evoked by “dad” (Figs. 6B, 7C).

We quantified the similarity of the patterns evoked by each consonant compared to “dad” in each individual rat using a Euclidean distance calculation as in our earlier studies (Engineer et al. 2008; Ranasinghe et al. 2012b). The similarity of neural response to consonants in A1 was slightly reduced in the moderate NE group compared to naïve controls ($p = 0.004$; Fig. 9). This result was most likely caused by the low-frequency map shift in the moderate NE group, since speech sounds are low frequency biased. As expected, the neural responses to speech in our intense NE group were poor (Fig. 6C). The only speech sounds that evoked a clear neural response (i.e., peak rate above 0.05 spikes/ms) were “dad” and “deed,” and these responses were mostly evoked in low-frequency tuned neurons (Fig. 7A). These neural responses were very weak for both high- and low-frequency tuned neurons ($p = 5.68\text{e-}4$ and $5.62\text{e-}9$ for low- and high-frequency responses to “dad”; Fig. 8B) and late in latency compared to the responses of normal controls or the moderate NE group ($p = 4.04\text{e-}7$ and $9.06\text{e-}50$ for low- and high-frequency responses to “dad”; Fig. 8A). The neural response to the consonants /b/ and /s/ were absent (Figs. 7B, C). We calculated the Euclidean distance between each initial consonant compared to “dad” in the intense NE group and found that each speech sound produced a neural response that was much less distinct than in naïve controls ($p = 1.96\text{e-}22$; Fig. 9). We also examined the neural responses in A1 to vowels in the moderate and intense NE groups. Our previous study demonstrated that the difficulty of vowel discrimination tasks is best predicted by looking at how the overall rate of response to each vowel differs in each individual site with no inclusion of temporal information (Perez et al. 2013). As in our earlier study, we calculated the average response rate during the entire vowel sound for each speech sound (300 ms). In the moderate NE group, the average rate of response to vowels was 0.015 ± 0.001 , which was not significantly different from the average response of 0.015 ± 0.0009 spikes/ms in controls ($p = 0.98$; Fig. 10B). Since neural responses to both vowels and consonants were robust in moderate NE rats, we predicted that these rats would be able to discriminate both vowels and consonants. In the intense NE group, the rate of response to vowels was dramatically smaller than in controls, only 0.0008 ± 0.0009 spikes/ms compared to 0.015 ± 0.0009 spikes/ms in controls ($p = 2.29\text{e-}11$; Fig. 10B). Since the intense NE group had degraded neural responses to both vowel and

consonant sounds, we predicted that the rats in the intense NE group would not be able to accurately discriminate speech sounds.

Behavioral Performance

We used a go/no-go task to evaluate how moderate and intense NE affected behavioral discrimination of speech sounds in two additional groups of rats. These rats were trained to discriminate speech sounds before NE so that their previous discrimination performance could be used as a baseline. We used the measure d' to quantify each animal's discrimination performance (Klein 2001). We also measured each rat's ability to discriminate three consonants ("bad," "tad," and "sad") and three vowels ("dud," "deed," and "dood") from the target "dad." A d' greater than 2 indicates accurate discrimination of these sounds. Before NE, the animals in all groups were able to discriminate both consonants and vowels from the target and had an average d' of 2.80 ± 0.21 for target versus silence, 2.09 ± 0.21 to consonants, and 2.28 ± 0.22 to vowels ($p = 0.63$ for target vs. silence, $p = 0.11$ for consonants, and $p = 0.10$ for vowels). These results are similar to the discrimination performance of other groups of animals that were trained on the same tasks for previous publications (Porter et al. 2011; Shetake et al. 2011; Ranasinghe et al. 2012b).

The moderate NE group had a transient decrease in discrimination performance when they were retested one month after NE. Although before NE the moderate NE group discriminated both vowels and consonants with an average d' of 2.44 ± 0.19 , after NE their discrimination performance fell to 2.06 ± 0.22 ($p = 0.18$, two-tailed paired t -test comparing before and after NE; Figs. 11A, B). Although there was a decrease in discrimination performance, the rats still showed robust discrimination of the speech sounds. After 2 weeks of training (recovery), the discrimination ability of this group of rats was not significantly different than before NE, at a d' of 2.78 ± 0.12 ($p = 0.13$, two-tailed paired t -test comparing before NE to after recovery; Fig. 11B). However, this group did demonstrate improved discrimination of the most difficult consonant and vowel distracters. The average discrimination performance on the sounds "tad" and "dud" improved from 1.72 ± 0.10 before NE to 2.17 ± 0.07 after recovery ($p = 0.006$, two-tailed t -test). However, discrimination of the other sounds ("sad," "bad," "deed," "dood") was largely unaltered (discrimination of other sounds; 2.96 ± 0.25 d' before NE; 3.05 ± 0.16 d' after recovery; $p = 0.75$, two-tailed t -test). These results demonstrate that the first type of NE tested (moderate NE) caused neural changes that were insufficient to impair speech discrimination and further discrimination training. Given the parameters of this NE type, these results are not surprising.

The intense NE group exhibited a severe loss in behavioral performance that did not recover after 2 weeks of discrimination testing. When the rats were first retested on the discrimination task one month after NE, their d' for discriminating the target from all speech sounds and even from silence was approximately zero (d' of 0.21 ± 0.13 for discrimination of all speech sounds; compared to 2.06 ± 0.22 before NE; $p = 3.41 \times 10^{-4}$; Fig. 11C, D). The rats in this group correctly hit in response to only $31.94 \pm 7.63\%$ of the targets that were presented (compared to $89.7 \pm 2.96\%$ before NE), indicating that the animal's poor performance was probably because they could not detect the presented sounds. After two

weeks of discrimination training, the rats were able to hear more of the “dad” sounds, and the d' of discrimination of the target versus silence went up to 1.24 ± 0.37 though this improvement failed to reach significance ($p = 0.06$; two-tailed t -test comparing performance immediately after NE and after recovery; Fig. 11D). At this point, the rats were able to hit to $68.94 \pm 4.16\%$ of the targets and $47.34 \pm 7.08\%$ of the distracter sounds, indicating that they had regained some ability to detect these sounds. The rats also went from pressing the lever during $8.28 \pm 3.34\%$ of silent trials before hearing loss to pressing during $24.48 \pm 7.55\%$ of silent trials after hearing loss and recovery. This weak discrimination performance and loss of behavioral control indicates that the rats' hearing was still very poor. These behavioral results are consistent with the severely degraded neural responses after intense NE.

DISCUSSION

Summary of Results

Moderate NE led to low-frequency map expansions and higher threshold, weaker responses for high-frequency tuned neurons in A1. This plasticity altered the pattern of activity evoked by complex speech sounds so that the patterns seen in A1 were different from naïve controls. However, these patterns were still distinct, and rats with moderate NE were readily able to perform operant discrimination tasks and discriminate speech sounds from one another. Intense NE obliterated the neural responses of most neurons in A1. The remaining sites had extremely high threshold responses. The neural responses to speech were similarly compromised, and rats were unable to discriminate speech sounds.

Moderate and Intense Noise Exposure

We have previously tested the hypothesis that behavioral discrimination is well correlated with the degree of similarity of the activity patterns evoked by speech sounds in the context of background noise, spectral degradation, temporal degradation, and cortical damage (Porter et al. 2011; Shetake et al. 2011; Ranasinghe et al. 2012b). The behavioral and physiological results from our moderate and intense NE groups expand this line of experiments to include speech discrimination after peripheral damage. Although there are important differences in the anatomy and physiology of rats and humans, the similarities reported across a wide range of experimental conditions demonstrate that the rat model is suitable for evaluating potential therapies for a variety of communication disorders. Recent advances in transgenic technology will make it possible to rapidly generate models of various genetic conditions in which central or peripheral alterations impair effective speech processing (Galaburda et al. 2006; Ohlemiller 2006; Geurts et al. 2009; Silverman et al. 2010).

Our study is the first to document how severe permanent hearing loss affected neural responses to speech and speech discrimination in rats. We used a high-intensity, low-frequency noise, which causes damage to a large portion of the cochlea in guinea pigs (Robertson & Johnstone 1980; Yamasoba et al. 1999). Although after intense NE rats were able to recover some rudimentary responses to tones and speech and were able to use those responses to detect speech sounds, they were not able to recover the ability to discriminate between speech sounds after two weeks of training.

The protocol used to induce temporary hearing loss in our experiment was very similar to the protocol used in several previous studies, and the results that we observed were similar as well. Previous studies have shown that exposure to a 16-kHz octave-band of noise for 1 hr leads to severely impaired hearing after 3 weeks (Syka & Rybalko 2000; Bauer 2003; Turner et al. 2006; Wang et al. 2009; Engineer et al. 2011; Yang et al. 2011; Browne et al. 2012). Over time, rats' hearing abilities and neural responses to tones recover, but substantial cortical plasticity is triggered by moderate NE. In our study, we observed that moderate NE led to low-frequency map reorganization and longer latencies in all sites in A1. This finding confirms several previous studies of NE in several different species and several different NE protocols (Robertson & Irvine 1989; Norena et al. 2003). This remaining plasticity may be caused by permanent degeneration of some fibers in the cochlear nerve (Kujawa & Liberman 2009).

One major difference between our study and previous studies is that previous studies have shown increased spontaneous firing rates in A1 after NE (Robertson & Irvine 1989; Eggermont & Komiyama 2000; Seki & Eggermont 2003), while we found that spontaneous firing rates were decreased. The reason for these differences might have been because the rats in our study had a relatively small increase in neural thresholds compared to previous studies in our own lab and in other labs even though they experienced the same NE protocol. Previous studies have indicated that the amount of spontaneous firing activity in auditory cortex increases as hearing thresholds increase as well (Eggermont & Komiyama 2000; Seki & Eggermont 2003). In previous publications by our own lab (Engineer et al. 2011), the rats included in the study were chosen to be animals that developed tinnitus after NE and may have been more severely affected by the NE protocol compared to the rats in our own study. In the present study, we included all rats that had experienced NE regardless of the amount of hearing damage that we observed. It is also possible that differences in anesthesia are responsible for the differences seen across studies. In the present study, we used pentobarbital anesthesia, which is commonly used in studies of auditory cortex responses and was used in our previous study on noise-induced tinnitus (Engineer et al. 2011). There is a high correlation between A1 responses to speech sounds and behavioral performance using both awake responses and pentobarbital anesthetized responses (Engineer et al. 2008; Centanni et al. 2014). The studies described above used pentobarbital to induce hearing loss (while our animals were exposed under ketamine and xylazine), and other studies have used a variety of methods during the assessment of cortical and subcortical firing after damage. Future studies should investigate the effects of different anesthetics on neural firing after noise trauma to eliminate this variable as the cause of cross-study differences.

The Effects of Hearing Loss on Speech Responses

Many earlier studies have shown that it can be quite difficult to predict the central consequences of cochlear damage. A recent clinical study confirmed that it is possible to have a positive cortical response in the absence of a detectable brainstem response (Kawase et al. 2014). Other clinical and animal studies have shown that cortical responses can be severely degraded when ABR thresholds are normal (Stach et al. 1994; Zhou et al. 2011). The goal of this study was to determine how peripheral damage alters the cortical representation of speech sounds.

Complex sounds such as speech evoke complicated spectro-temporal patterns across the cortex. Within the auditory cortex, previous studies have also shown that latencies and response strengths in response to speech are altered by NE and hearing loss. For example, the neural responses to a “ba”/“pa” continuum were altered in cats after NE. The evoked response to the speech sounds was smaller, and latencies were longer after NE than in naïve controls (Tomita et al. 2004; Aizawa & Eggermont 2006). In our own study, we found that latencies were longer and the evoked responses to speech sounds were smaller for a wide variety of speech sounds. We also observed that after NE, the latency of responses to speech sounds was more strongly affected than the latency of responses to tones. While the peak latency in response to tones was only about 2 ms longer after NE, the peak latency in response to speech sounds was 7–10 ms longer in the moderate NE group. This finding supports the conclusion that the neural response to complex sounds such as speech was more strongly affected than the response to simple stimuli such as tones. Differences in rise time may be partly responsible (Heil 2001). Previous studies have indicated that after NE, the balance of excitation and inhibition is permanently altered in the auditory cortex (Milbrandt et al. 2000; Zettel et al. 2003; Alvarado et al. 2005; Tan et al. 2007; Dong et al. 2009; Browne et al. 2012). This change in the basic “wiring” of the auditory cortex appears to have more extensive effects on speech sounds than tones. In previous studies, we have shown that there is a strong correlation between the Euclidean distance of pairs of neural response patterns and behavioral discrimination performance on the same task (Engineer et al. 2008; Shetake et al. 2011; Ranasinghe et al. 2012b; Centanni et al. 2013a; Perez et al. 2013). Speech responses in A1 are not enhanced after weeks of speech training (Engineer et al. 2014). In the present study, we saw that intense NE significantly decreased the average Euclidean distance across pairs of neural patterns compared to rats in the control and moderate NE groups. Though we did not have enough responsive sites in the present study to directly compare Euclidean distance and behavior on each pair of sounds, our previous work suggests that there would be a strong correlation across the three groups tested, and any future studies should include this type of analysis.

Several previous studies have also documented how moderate NE affects neural responses to speech sounds across the auditory pathway. Hearing loss changes how all stations of the auditory system respond to either vowels or consonants (Palmer & Moorjani 1993; Miller et al. 1997; Schilling et al. 1998; Miller et al. 1999a, b; Zilany & Bruce 2007). For example, rate information in the auditory nerve is greatly degraded after acoustic trauma, while information that could allow discrimination remains in the temporal aspects of the responses (Miller et al. 1999b; Kale & Heinz 2010; Young 2012). Such a change at the subcortical level would likely disrupt the precision of coding higher up in the auditory pathway and may be responsible for the degraded neural patterns we observed in this study.

In the cortex, the loss of hearing acuity is correlated with a decrease in gray matter volume (Peelle et al. 2011). In the present study, we produced two different levels of hearing loss by altering both the frequency and the intensity of the noise during NE. Future studies should systematically examine the effects of altering frequency and intensity of NE on tone and speech responses and should also clarify how peripheral versus central factors lead to changed responses to speech and other complex sounds after NE. Future studies should also compare neural responses across cortical layers following NE. There may be an effect of

cortical layer on the level of degradation seen. Cortical layer 3, for example, projects to downstream cortical areas and responses in this lamina may also provide insight into the effects of NE on neural networks.

BEHAVIORAL DISCRIMINATION AFTER HEARING LOSS

We found that after moderate NE, rats still had good behavioral discrimination of consonants and vowels. Despite reduced response strength and longer response latency, cortical responses to speech were still sufficient to support accurate discrimination. This result was comparable to our earlier observation that degraded frequency selectivity and altered phase-locking to temporally modulated sounds does not impair speech discrimination (Ranasinghe et al. 2012a). Some previous studies in humans have also shown that subjects with hearing loss can readily discriminate consonants (Johnson et al. 1984; Phillips et al. 1994), although in other studies subjects with hearing loss have difficulty (Smoorenburg 1992; Peelle et al. 2011). The differences in findings are likely due to differences in methods as well as the amount of hearing loss suffered by each group of listeners (Cervera et al. 2009).

The intense NE group had great difficulties responding to speech sounds after NE. In the present study, our speech stimuli were only presented at 60 dB, and it is likely that hearing thresholds in the intense NE group were so high that the 60 dB sounds were barely audible. Future studies should address whether increasing the intensity of the speech sounds during behavioral testing improves detection and discrimination performance. The intense NE group did have slightly improved detection abilities after 2 weeks of testing, so it would also be interesting to test whether long courses of behavioral training or other interventions such as vagus nerve or nucleus basalis stimulation pairing could lead to neural plasticity that improved behavioral outcomes (Engineer et al. 2011; Reed et al. 2011).

CONCLUSIONS

This study evaluated the effects of either moderate or intense NE on neural and behavioral responses to speech sounds in rats. Similar to humans, we found that moderate NE did not impair speech discrimination abilities, but intense NE had severe effects on both neural and behavioral responses to speech sounds. Rats make a favorable model of speech sound processing, and the development of future transgenic models will make it possible to evaluate speech sound processing in a variety of conditions known to cause human disease.

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REFERENCES

- Aizawa N, Eggermont JJ. Effects of noise-induced hearing loss at young age on voice onset time and gap-in-noise representations in adult cat primary auditory cortex. *J Assoc Res Otolaryngol.* 2006; 7:71–81. [PubMed: 16408166]

- Alvarado JC, Fuentes-Santamaria V, Franklin SR, et al. Uni-lateral cochlear ablation in adult ferrets results in upregulation in calretinin immunostaining in the central nucleus of the inferior colliculus. *Neuroscience*. 2005; 136:957–969. [PubMed: 16344163]
- Axelsson A, Sandh A. Tinnitus in noise-induced hearing loss. *Br J Audiol*. 1985; 19:271–276. [PubMed: 4074979]
- Bauer CA. Animal models of tinnitus. *Otolaryngol Clin North Am*. 2003; 36:267–285. vi. [PubMed: 12856296]
- Blamey PJ, Sarant JZ, Paatsch LE, et al. Relationships among speech perception, production, language, hearing loss, and age in children with impaired hearing. *J Speech Lang Hear Res*. 2001; 44:264–285. [PubMed: 11324650]
- Boothroyd A. Auditory perception of speech contrasts by subjects with sensorineural hearing loss. *J Speech Hear Res*. 1984; 27:134–144. [PubMed: 6716999]
- Browne CJ, Morley JW, Parsons CH. Tracking the expression of excitatory and inhibitory neurotransmission-related proteins and neuroplasticity markers after noise induced hearing loss. *PLoS One*. 2012; 7:e33272. [PubMed: 22428005]
- Centanni TM, Engineer CT, Kilgard MP. Cortical speech-evoked response patterns in multiple auditory fields are correlated with behavioral discrimination ability. *J Neurophysiol*. 2013a; 110:177–189. [PubMed: 23596332]
- Centanni TM, Sloan AM, Reed AC, et al. Detection and identification of speech sounds using cortical activity patterns. *Neuroscience*. 2013b; 258:292–306. doi: 10.1016/j.neuroscience.2013.11.030. [PubMed: 24286757]
- Centanni TM, Sloan AM, Reed AC, et al. Detection and identification of speech sounds using cortical activity patterns. *Neuroscience*. 2014; 258:292–306. [PubMed: 24286757]
- Cervera TC, Soler MJ, Dasi C, et al. Speech recognition and working memory capacity in young-elderly listeners: Effects of hearing sensitivity. *Can J Exp Psychol*. 2009; 63:216–226. [PubMed: 19739905]
- Dong S, Mulders WH, Rodger J, et al. Changes in neuronal activity and gene expression in guinea-pig auditory brainstem after uni-lateral partial hearing loss. *Neuroscience*. 2009; 159:1164–1174. [PubMed: 19356697]
- Eggermont JJ, Komiya H. Moderate noise trauma in juvenile cats results in profound cortical topographic map changes in adulthood. *Hear Res*. 2000; 142:89–101. [PubMed: 10748332]
- Engineer CT, Perez CA, Chen YH, et al. Cortical activity patterns predict speech discrimination ability. *Nat Neurosci*. 2008; 11:603–608. [PubMed: 18425123]
- Engineer CT, Perez CA, Carraway RS, et al. Similarity of cortical activity patterns predicts generalization behavior. *PloS one*. 2013; 8(10):e78607. [PubMed: 24147140]
- Engineer CT, Centanni TM, Im KW, et al. Degraded auditory processing in a rat model of autism limits the speech representation in non-primary auditory cortex. *Dev Neurobiol*. 2014a doi: 10.1002/dneu.22175.
- Engineer CT, Perez CA, Carraway RS, et al. Speech training alters tone frequency tuning in rat primary auditory cortex. *Behav Brain Res*. 2014b; 258:166–178. [PubMed: 24344364]
- Engineer ND, Riley JR, Seale JD, et al. Reversing pathological neural activity using targeted plasticity. *Nature*. 2011; 470:101–104. [PubMed: 21228773]
- Galaburda AM, LoTurco J, Ramus F, et al. From genes to behavior in developmental dyslexia. *Nat Neurosci*. 2006; 9:1213–1217. [PubMed: 17001339]
- Geurts AM, Cost GJ, Freyvert Y, et al. Knockout rats via embryo microinjection of zinc-finger nucleases. *Science*. 2009; 325:433. [PubMed: 19628861]
- Green, DM.; Swets, JA. *Signal Detection Theory and Psychophysics*. Vol. 1. Wiley; New York, NY: 1966.
- Heil P. Representation of sound onsets in the auditory system. *Audiol Neurotol*. 2001; 6:167–172. [PubMed: 11694721]
- Helfer KS, Wilber LA. Hearing loss, aging, and speech perception in reverberation and noise. *J Speech Hear Res*. 1990; 33:149–155. [PubMed: 2314073]

- Johnson D, Whaley P, Dorman MF. Processing of cues for stop consonant voicing by young hearing-impaired listeners. *J Speech Hear Res.* 1984; 27:112–118. [PubMed: 6716995]
- Kale S, Heinz MG. Envelope coding in auditory nerve fibers following noise-induced hearing loss. *J Assoc Res Otolaryngol.* 2010; 11:657–673. [PubMed: 20556628]
- Kawahara H. Speech representation and transformation using adaptive interpolation of weighted spectrum: Vocoder revisited. *IEEE.* 1997; 2:1303–1306.
- Kawase T, Kanno A, Takata Y, et al. Positive auditory cortical responses in patients with absent brainstem response. *Clin Neurophysiol.* 2014; 125(1):148–153. [PubMed: 23895952]
- Kilgard MP, Merzenich MM. Cortical map reorganization enabled by nucleus basalis activity. *Science.* 1998; 279:1714–1718. [PubMed: 9497289]
- Kilgard MP, Merzenich MM. Distributed representation of spectral and temporal information in rat auditory cortex. *Hear Res.* 1999; 134:16–28. [PubMed: 10452372]
- Klein SA. Measuring, estimating, and understanding the psycho-metric function: a commentary. *Percept Psychophys.* 2001; 63:1421–1455. [PubMed: 11800466]
- Kluender KR, Diehl RL, Killeen PR. Japanese quail can learn phonetic categories. *Science.* 1987; 237:1195–1197. [PubMed: 3629235]
- Kuhl PK, Miller JD. Speech perception by the chinchilla: voiced-voiceless distinction in alveolar plosive consonants. *Science.* 1975; 190:69–72. [PubMed: 1166301]
- Kujawa SG, Liberman MC. Adding insult to injury: cochlear nerve degeneration after “temporary” noise-induced hearing loss. *J Neurosci.* 2009; 29:14077–14085. [PubMed: 19906956]
- Lorenzi C, Gilbert G, Carn H, et al. Speech perception problems of the hearing impaired reflect inability to use temporal fine structure. *Proc Natl Acad Sci USA.* 2006; 103:18866–18869. [PubMed: 17116863]
- Milbrandt JC, Holder TM, Wilson MC, et al. GAD levels and muscimol binding in rat inferior colliculus following acoustic trauma. *Hear Res.* 2000; 147:251–260. [PubMed: 10962189]
- Miller RL, Calhoun BM, Young ED. Contrast enhancement improves the representation of /epsilon/-like vowels in the hearing-impaired auditory nerve. *J Acoust Soc Am.* 1999; 106:2693–2708. [PubMed: 10573886]
- Miller RL, Calhoun BM, Young ED. Discriminability of vowel representations in cat auditory-nerve fibers after acoustic trauma. *J Acoust Soc Am.* 1999; 105:311–325. [PubMed: 9921658]
- Miller RL, Schilling JR, Franck KR, et al. Effects of acoustic trauma on the representation of the vowel “eh” in cat auditory nerve fibers. *J Acoust Soc Am.* 1997; 101:3602–3616. [PubMed: 9193048]
- Moscicki EK, Elkins EF, Baum HM, et al. Hearing loss in the elderly: An epidemiologic study of the Framingham Heart Study Cohort. *Ear Hear.* 1985; 6:184–190. [PubMed: 4043571]
- Noreña AJ, Eggermont JJ. Enriched acoustic environment after noise trauma reduces hearing loss and prevents cortical map reorganization. *J Neurosci.* 2005; 25:699–705. [PubMed: 15659607]
- Noreña AJ, Eggermont JJ. Enriched acoustic environment after noise trauma abolishes neural signs of tinnitus. *Neuroreport.* 2006; 17:559–563. [PubMed: 16603911]
- Noreña AJ, Tomita M, Eggermont JJ. Neural changes in cat auditory cortex after a transient pure-tone trauma. *J Neurophysiol.* 2003; 90:2387–2401. [PubMed: 12773493]
- Ohlemiller KK. Contributions of mouse models to understanding of age- and noise-related hearing loss. *Brain Res.* 2006; 1091:89–102. [PubMed: 16631134]
- Palmer AR, Moorjani PA. Responses to speech signals in the normal and pathological peripheral auditory system. *Prog Brain Res.* 1993; 97:107–115. [PubMed: 8234737]
- Peelle JE, Troiani V, Grossman M, et al. Hearing loss in older adults affects neural systems supporting speech comprehension. *J Neurosci.* 2011; 31:12638–12643. [PubMed: 21880924]
- Perez CA, Engineer CT, Jakkamsetti V, et al. Different times-cales for the neural coding of consonant and vowel sounds. *Cereb Cortex.* 2013; 23:670–83. [PubMed: 22426334]
- Phillips DP, Rappaport JM, Gulliver JM. Impaired word recognition in noise by patients with noise-induced cochlear hearing loss: Contribution of temporal resolution defect. *Am J Otol.* 1994; 15:679–686. [PubMed: 8572072]

- Plomp R. Auditory handicap of hearing impairment and the limited benefit of hearing aids. *J Acoust Soc Am.* 1978; 63:533–549. [PubMed: 670550]
- Polley DB, Read HL, Storace DA, et al. Multiparametric auditory receptive field organization across five cortical fields in the albino rat. *J Neurophysiol.* 2007; 97:3621–3638. [PubMed: 17376842]
- Porter BA, Rosenthal TR, Ranasinghe KG, et al. Discrimination of brief speech sounds is impaired in rats with auditory cortex lesions. *Behav Brain Res.* 2011; 219:68–74. [PubMed: 21167211]
- Ranasinghe KG, Carraway RS, Borland MS, et al. Speech discrimination after early exposure to pulsed-noise or speech. *Hear Res.* 2012a; 289:1, 12. [PubMed: 22575207]
- Ranasinghe KG, Vrana WA, Matney CJ, et al. Neural mechanisms supporting robust discrimination of spectrally and temporally degraded speech. *J Assoc Res Otolaryngol.* 2012b; 13:527–542. [PubMed: 22549175]
- Reed A, Riley J, Carraway R, et al. Cortical map plasticity improves learning but is not necessary for improved performance. *Neuron.* 2011; 70:121–131. [PubMed: 21482361]
- Reed P, Howell P, Sackin S, et al. Speech perception in rats: Use of duration and rise time cues in labeling of affricate/fricative sounds. *J Exp Anal Behav.* 2003; 80:205–215. [PubMed: 14674729]
- Robertson D, Irvine DR. Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. *J Comp Neurol.* 1989; 282:456–471. [PubMed: 2715393]
- Robertson D, Johnstone BM. Acoustic trauma in the guinea pig cochlea: Early changes in ultrastructure and neural threshold. *Hear Res.* 1980; 3:167–179. [PubMed: 7419484]
- Schilling JR, Miller RL, Sachs MB, et al. Frequency-shaped amplification changes the neural representation of speech with noise-induced hearing loss. *Hear Res.* 1998; 117:57–70. [PubMed: 9557978]
- Seki S, Eggermont JJ. Changes in cat primary auditory cortex after minor-to-moderate pure-tone induced hearing loss. *Hear Res.* 2002; 173:172–186. [PubMed: 12372645]
- Seki S, Eggermont JJ. Changes in spontaneous firing rate and neural synchrony in cat primary auditory cortex after localized tone-induced hearing loss. *Hear Res.* 2003; 180:28–38. [PubMed: 12782350]
- Shetake JA, Wolf JT, Cheung RJ, et al. Cortical activity patterns predict robust speech discrimination ability in noise. *Eur J Neurosci.* 2011; 34:1823–1838. [PubMed: 22098331]
- Silverman JL, Yang M, Lord C, et al. Behavioural pheno-typing assays for mouse models of autism. *Nat Rev Neurosci.* 2010; 11:490–502. [PubMed: 20559336]
- Smooenburg GF. Speech reception in quiet and in noisy conditions by individuals with noise-induced hearing loss in relation to their tone audiogram. *J Acoust Soc Am.* 1992; 91:421–437. [PubMed: 1737889]
- Stach BA, Stoner WR, Smith SL, et al. Auditory evoked potentials in Rett syndrome. *J Am Acad Audiol.* 1994; 5(3):226–230. [PubMed: 8075419]
- Steinschneider M, Schroeder CE, Arezzo JC, et al. Speech-evoked activity in primary auditory cortex: Effects of voice onset time. *Electroencephalogr Clin Neurophysiol.* 1994; 92:30–43. [PubMed: 7508851]
- Steinschneider M, Volkov IO, Noh MD, et al. Temporal encoding of the voice onset time phonetic parameter by field potentials recorded directly from human auditory cortex. *J Neurophysiol.* 1999; 82:2346–2357. [PubMed: 10561410]
- Syka J, Rybalko N. Threshold shifts and enhancement of cortical evoked responses after noise exposure in rats. *Hear Res.* 2000; 139:59–68. [PubMed: 10601713]
- Tan J, Ruttiger L, Panford-Walsh R, et al. Tinnitus behavior and hearing function correlate with the reciprocal expression patterns of BDNF and Arg3.1/arc in auditory neurons following acoustic trauma. *Neuroscience.* 2007; 145:715–726. [PubMed: 17275194]
- Tomita M, Noreña AJ, Eggermont JJ. Effects of an acute acoustic trauma on the representation of a voice onset time continuum in cat primary auditory cortex. *Hear Res.* 2004; 193:39–50. [PubMed: 15219319]
- Turner JG, Brozoski TJ, Bauer CA, et al. Gap detection deficits in rats with tinnitus: a potential novel screening tool. *Behav Neurosci.* 2006; 120:188–195. [PubMed: 16492129]
- Wang H, Brozoski TJ, Turner JG, et al. Plasticity at glycinergic synapses in dorsal cochlear nucleus of rats with behavioral evidence of tinnitus. *Neuroscience.* 2009; 164:747–759. [PubMed: 19699270]

- Yamasoba T, Schacht J, Shoji F, et al. Attenuation of cochlear damage from noise trauma by an iron chelator, a free radical scavenger and glial cell line-derived neurotrophic factor in vivo. *Brain Res.* 1999; 815:317–325. [PubMed: 9878807]
- Yang S, Weiner BD, Zhang LS, et al. Homeostatic plasticity drives tinnitus perception in an animal model. *Proc Natl Acad Sci USA.* 2011; 108:14974–14979. [PubMed: 21896771]
- Young, ED. Neural coding of sound with cochlear damage.. In: Henderson, D.; LePrell, CG., editors. *Noise-Induced Hearing Loss: Scientific Advances.* Springer; New York, NY: 2012. p. 87-135.
- Zettel ML, O'Neill WE, Trang TT, et al. The effects of early bilateral deafening on calretinin expression in the dorsal cochlear nucleus of aged CBA/CaJ mice. *Hear Res.* 2003; 183:57–66. [PubMed: 13679138]
- Zhou X, Panizzutti R, de Villers-Sidani É, et al. Natural restoration of critical period plasticity in the juvenile and adult primary auditory cortex. *J Neurosci.* 2011; 31(15):5625–5634. [PubMed: 21490203]
- Zilany MS, Bruce IC. Representation of the vowel /epsilon/ in normal and impaired auditory nerve fibers: model predictions of responses in cats. *J Acoust Soc Am.* 2007; 122:402–417. [PubMed: 17614499]

Fig. 1. Moderate and intense noise exposure (NE) elevated auditory brainstem response (ABR) thresholds. The intense NE group ($n = 2$ rats) had more ABR threshold elevation than the moderate NE group ($n = 3$ rats) or the control group ($n = 4$ rats). Average thresholds are plotted for 4, 10, 16, and 32 kHz tones. ABRs were recorded under pentobarbital anesthesia, as described in our previous study (Engineer et al. 2011). Error bars represent SEM across rats.

Fig. 2.

Moderate and intense noise exposure (NE) changed basic neural responses to tones. Each panel shows tuning curve responses collected from one representative site in each group that is tuned to a mid-frequency (4–9 kHz). Each successive type of NE reduced firing to lower intensity tones. A, Representative site's response to tones from a naïve control animal. B, Representative site's response to tones in an animal with moderate NE (1 hr exposure to 115 dB SPL 16 kHz 1-octave noise band). After this level of NE, responses to the softest intensity tones were decreased compared to controls. C, Representative site's response to tones in an animal with intense NE (1 hr exposure to 125 dB SPL 4 kHz 1-octave noise band). After this level of NE, neurons responded only to the loudest intensity tones.

Fig. 3.

Moderate and intense noise exposure (NE) changed the tonotopic organization of responses in the auditory cortex. Each panel shows data collected from one representative animal in each experimental group. Each polygon represents a single electrode penetration into the auditory cortex. The color of the polygon represents the characteristic frequency of each penetration. Sites marked with an “o” were assigned to fields other than A1; sites marked with an “x” were classified as nonresponsive to tones. A, Representative map of a naïve control animal. B, Representative map of an animal with moderate NE. There were more low-frequency tuned sites for this animal (i.e., sites that are colored yellow) and fewer high-frequency tuned sites (sites that are colored purple) than in the naïve control animal. C, Representative map of an animal with intense NE. This animal had very few sites that were still tuned and responsive to tones compared to the control and moderate NE rat.

Fig. 4.

Moderate and intense noise exposure (NE) changed response properties of A1 neurons. **A**, The average percentage of the area of A1 cortex that responded to each frequency from 1 to 32 kHz at 60 dB SPL was calculated for each rat in each experimental group. The shaded region behind each line indicates the standard error of the mean (SEM). The horizontal lines at the top of the plot indicate frequencies at which the control and moderate NE group were significantly different from one another. The intense NE group was significantly different from controls at all presented frequencies. **B**, The average threshold for low- or high-frequency tuned sites in each experimental group. Error bars indicate SEM. *** $p < 0.001$ (compared to control group). **C**, Average poststimulus time histogram in response to all presented tones for low- and high-frequency tuned sites for each experimental group. The spontaneous firing rate for each group was subtracted out of each poststimulus time histogram. **D**, Average spontaneous firing rate for low- and high-frequency tuned sites for each experimental group. Error bars indicate SEM. *** $p < 0.001$ (compared to control group).

Fig. 5.

Response properties of A1 sites in each of the three experimental groups. A, Noise exposure (NE) significantly increased onset latency in both moderate and intense NE groups. $***p < 0.001$ (compared to control group). B, Intense NE caused a significant decrease in the number of driven spikes to tones while moderate NE did not significantly decrease driven spikes. $***p < 0.001$ (compared to control group). C, Threshold significantly increased in both the moderate NE and intense NE groups. $***p < 0.001$ (compared to control group). D, Intense NE decreased bandwidth compared to controls, while moderate NE did not affect bandwidths. $***p < 0.001$ (compared to control group).

Fig. 6.

Spatiotemporal response patterns are degraded after moderate and intense noise exposure (NE). Neurograms show the average poststimulus time histogram and raw neural responses for all experimental sites in each experimental group. In each panel, the average poststimulus time histogram is shown at the top of the plot. Each individual site was sorted by characteristic frequency (based on tone responses) and then the response to the consonant by each individual site is plotted. Darker colors indicate a stronger response to the speech sound at each time point. The zero point on each plot was chosen based on the average onset response for each consonant in control sites. Only sites that had significant tone responses were included in this figure. A, The responses from all control sites to the consonants “dad,” “sad,” and “bad.” B, The responses from all sites from the moderate NE group to the consonants “dad,” “sad,” and “bad.” C, The responses from all sites from the intense NE group to the consonants “dad,” “sad,” and “bad.”

Fig. 7.

Speech sounds produced altered patterns of activity after both moderate and intense noise exposure. The poststimulus time histogram in response to speech sounds is plotted for low- and high-frequency tuned sites. Each poststimulus time histogram shows 60 ms of activity. 0 ms in each plot indicates the expected onset latency of responses based on control data. A, “Dad” activated both low- and high-frequency tuned neurons, but high-frequency tuned neurons responded more quickly. After intense noise exposure, this is one of the only speech sounds to still evoke neural activity. B, “Sad” activates more activity in high-frequency

tuned neurons than low-frequency tuned neurons. C, “Bad” activates more activity in low-frequency tuned neurons than in high-frequency tuned neurons.

Fig. 8.

Moderate and intense noise exposure led to increased latencies and decreased response strengths in response to speech sounds. Error bars in all plots show SEM. *** $p < 0.001$ (compared to control group). A, The average peak latency in response to the speech sound “dad” for low- and high-frequency tuned sites for all three experimental groups. B, The driven response (average of the first 40 ms after onset latency) for low- and high-frequency tuned sites to the speech sound “dad” for all three experimental groups.

Fig. 9.

Intense noise exposure significantly increased the neural similarity of responses to consonants. Neural similarity was calculated by determining the Euclidean distance between the neural response to “dad” and the neural response to all the other presented speech sounds. The Euclidean distance calculated during spontaneous firing when no stimulus was present was subtracted for each of the three groups. Error bars indicate SEM. *** $p < 0.001$ (compared to control group).

Fig. 10.

Moderate noise exposure did not change neural responses to vowels, but intense noise exposure decreased neural responses to vowels. A, Example of poststimulus time histogram in response to the consonant “dad” showing both consonant (0–60 ms) and vowel response (60–360 ms). B, The average driven response rate to all vowel sounds was calculated for all three groups (the spontaneous firing rate was subtracted from the response rate). *** $p < 0.001$ (compared to control group). Error bars indicate SEM.

Fig. 11.

Behavioral discrimination of speech sounds was altered by intense noise exposure (NE) but not affected by moderate NE. Error bars in all plots indicate SEM. A, Time course of the discrimination of speech sounds by rats that experienced moderate NE. The break after pretraining and NE was 1 month long. B, Average performance of the moderate NE group during the 3 days previous to NE (before), days 2–4 after NE (after), and the last 3 days of post-testing (recovery). C, Time course of the discrimination of speech sounds by rats that experienced intense NE. The break after pretraining and NE post-testing was 1 month long. D, Average performance of the intense NE group during the 3 days previous to NE (before), days 2–4 after NE (after), and the last 3 days of post-testing (recovery). * indicates that all types of discriminations (target detection and consonant and vowel discrimination) were significantly worse during the after and recovery periods compared to the before time period ($p < 0.05$).

TABLE 1

Description of the number of rats used in this study by experimental group

Group	Experimentally Naïve (Neural Recordings Only) (N)	Behaviorally Trained (N)
Control	6	0
Moderate	5	4
Intense	4	3
Total	15	7

TABLE 2

Number and proportion of recording sites classified as responsive or nonresponsive for each experimental group

Group	Total Sites	A1 Sites (%)	Other Fields (%)	Nonresponsive (%)
Control (<i>n</i> = 6)	62.33 ± 8.28	45.83 ± 7.58 (71.14 ± 6.09%)	11.33 ± 3.20 (17.11 ± 3.29%)	5 ± 1.81 (11.53 ± 7.0%)
Moderate (<i>n</i> = 5)	64.00 ± 5.83	43.2 ± 3.65 (68.06 ± 4.84%)	15.6 ± 4.04 (23.73 ± 4.96%)	5 ± 3.64 (7.86 ± 6.24%)
Intense (<i>n</i> = 4)	66.5 ± 3.70	15.25 ± 5.97 ^{**} (23.04 ± 8.36%)	1.15 ± 1.11 [*] (2.22 ± 1.57%)	49.25 ± 7.69 ^{**} (73.91 ± 9.57%)

*
p < 0.01

**
p < 0.001, two-tailed t-test.