Research Article

Dorsal Cochlear Nucleus of the Rat: Representation of Complex Sounds in Ears Damaged by Acoustic Trauma

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ABSTRACT

Acoustic trauma damages the cochlea but secondarily modifies circuits of the central auditory system. Changes include decreases in inhibitory neurotransmitter systems, degeneration and rewiring of synaptic circuits, and changes in neural activity. Little is known about the consequences of these changes for the representation of complex sounds. Here, we show data from the dorsal cochlear nucleus (DCN) of rats with a moderate high-frequency hearing loss following acoustic trauma. Single-neuron recording was used to estimate the organization of neurons' receptive fields, the balance of inhibition and excitation, and the representation of the spectra of complex broadband stimuli. The complex stimuli had random spectral shapes (RSSs), and the responses were fit with a model that allows the quality of the representation and its degree of linearity to be estimated. Tone response maps of DCN neurons in rat are like those in other species investigated previously, suggesting the same general organization of this nucleus. Following acoustic trauma, abnormal response types appeared. These can be interpreted as reflecting degraded tuning in auditory nerve fibers plus loss of inhibitory inputs in DCN. Abnormal types are somewhat more prevalent at later times (103–376 days) following the exposure, but not significantly so. Inhibition became weaker in post-trauma neurons that retained inhibitory responses but also disappeared in many neurons. The quality of the representation of spectral shape,

measured by sensitivity to the spectral shapes of RSS stimuli, was decreased following trauma; in fact, neurons with abnormal response types responded mainly to overall stimulus level, and not spectral shape.

Keywords: rat, dorsal cochlear nucleus, response map, acoustic trauma, inhibition, random spectral shape, model, neuropathy

INTRODUCTION

Although it is clear that changes in the circuits of the central auditory system occur following acoustic trauma (Syka 2002; Gold and Bajo 2014), the consequences of these changes for representation of broadband and spectrally complex sounds are unknown. Central neurons in cochlea-damaged animals may show threshold elevation and broadening of tuning, secondary to hair cell damage and consequent changes in auditory nerve fiber responses (Liberman and Dodds 1984; Miller et al. 1997; Young 2011). In addition, it is now clear that sound exposure produces substantial loss of hair cell/spiral ganglion synapses and degeneration of auditory nerve fibers, independent of hair cell damage (Kujawa and Liberman 2009; Tagoe et al. 2014). This degeneration, along with the decrease in spontaneous and sound-driven activity in surviving fibers, leads to changes in central circuits. Examples of such changes include degeneration and reorganization of synaptic circuits in the cochlear nucleus (Kim et al. 2004; Du et al. 2012; Browne et al. 2012), weakening of inhibitory versus excitatory

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circuits (Mossop et al. 2000; Vale and Sanes 2002; Wang et al. 2009; Whiting et al. 2009; Xie and Manis 2013), and changes in the relative strength of auditory and non-auditory synaptic inputs (Shore et al. 2008; Barker et al. 2012; Zeng et al. 2012). These circuit changes cause reorganization of synaptic processing (Ma and Young 2006; Pilati et al. 2012) that may degrade the representation of sound. Sometimes such changes in central neurons can be related to perceptual deficits in hearing impairment. Examples of the latter include abnormalities in loudness recruitment related to enhanced response rates in central nuclei (Syka 2002; Cai et al. 2009) and tinnitus related to increases in spontaneous activity (reviewed by Eggermont and Roberts 2014; Kaltenbach et al. 2005).

The dorsal cochlear nucleus (DCN) is a useful site for investigation of central reorganization following cochlear damage because of its relatively well-characterized neuronal circuitry, which includes substantial inhibition (reviewed by Young and Davis 2001). The DCN's inhibitory interneurons participate in generating its unusual responses to particular sounds, such as the sensitivity to spectral notches and spectral edges (Nelken and Young 1997; Reiss and Young 2005; Bandyopadhyay et al. 2007), so the status of those inhibitory circuits following acoustic trauma is of interest.

There has been limited study of the representation of sound, especially complex sounds, in the DCN following acoustic trauma, focusing mostly on response types for tonal stimuli (Caspary et al. 2005; Ma and Young 2006; Finlayson and Kaltenbach 2009; Pilati et al. 2012), effects of trauma on non-auditory inputs to DCN (Shore et al. 2008; Dehmel et al. 2012), and temporal coding (Schattelman et al. 2008). The goal of the present work was to characterize the changes in inhibition and spectral processing of complex stimuli in single neurons of DCN following acoustic trauma. Because the neural circuits change over a period of months (Kim et al. 2004; Kujawa and Liberman 2009; Browne et al. 2012), neuron recordings were done from 103 to 376 days after sound exposure. Inhibitory responses were changed in strength, differently for different response types, and were lost in many neurons. Complex stimulus representation was degraded, especially in neurons without inhibition.

MATERIALS AND METHODS

Animal Preparation, Acoustic Trauma, Recording

Experiments were done on adult male Sprague-Dawley rats (300–600 g) from Harlan Laboratories (Indianapolis, IN) using a protocol conforming to the National Institute of Health Guidelines for the Use

and Care of Laboratory Animals; the protocol was approved by the Johns Hopkins Animal Care and Use Committee. The data shown here were obtained from 24 rats, 13 unexposed and 11 exposed to acoustic trauma.

For sound exposure, the rats were anesthetized with ketamine (95 mg/kg im) and xylazine (5 mg/kg im). The exposures were varied over a narrow range giving a 50–60-dB high-frequency threshold shift (ABR), and the recovery times between exposure and neural recording were also varied. Rats were placed in a cylindrical cage suspended in the middle of a sound-proofed chamber (IAC) arranged so one ear was oriented toward the speaker. The other ear was plugged. The exposure stimulus was an octave band of noise centered at 16 kHz, 1–2 h in duration, at 114 or 116.5-dB SPL free-field sound level (Pyramid TW57 tweeter). ABRs were obtained before and after exposure (1 day before, 1 and 2 weeks after, and 1 day prior to single-neuron recording, in each animal). The rat was anesthetized as above, and electrodes were placed in the skin over the exposed-side bulla and the vertex, with a ground on the leg. The unexposed ear was plugged. Thresholds were measured for clicks and tone bursts (0.5 ms rise/fall, 5 ms duration, 30 bursts/s) between 2 and 40 kHz. Five hundred repetitions were averaged, and the ABR threshold (2 SD relative to background) determined as by Ngan and May (2001).

Single-neuron recording was done from 103 to 376 days after sound exposure. For recording, the rat was anesthetized with ketamine/xylazine (95/10 mg/kg im); supplemental doses were given as needed to maintain anesthesia through the recording session. In addition, 0.06 mg of atropine (im) was given to reduce mucous secretions and 0.18 mg of dexamethasone (ip) to reduce tissue edema. The core body temperature was monitored rectally and maintained at 36.5–37 °C. A screw was attached to the skull with small screws and dental cement; the larger screw was ~3 mm posterior to the bregma and was used to hold the head during recording, along with one (nonpuncturing) earbar in the ear contralateral to recording.

In control rats, recording was done on the left side; in exposed rats, it was done on the side ipsilateral to the sound-exposed ear (not always the left). The DCN was reached through a 5×5 mm hole centered 4 mm posterior to the interaural line and 3.5 mm lateral to the midline. A tungsten electrode ($\approx 5\text{ M}\Omega$, A-M Systems) was driven stereotactically to the DCN (Paxinos and Watson 1997). The surface of the DCN was determined from the sudden increase in the amplitude of the neural response to broadband noise bursts. The DCN can be distinguished from VCN by neuron response

properties, mainly the lack of type II and IV neuron responses in VCN and the lack of type I neuron recordings in DCN (Shofner and Young 1985).

Acoustic Stimuli, Experimental Protocol

Sound stimuli were presented in free-field from a tweeter (Fostex FT28D) placed ~30–50 cm lateral to the ear on the side ipsilateral to the microelectrode recording. The acoustic stimulus was calibrated using a 0.25-in. Bruel and Kjaer microphone suspended just lateral to the intact pinna of the rat. The average acoustic calibration across experiments is shown by the black curve in Figure 1A; note that the stimulus contained little energy above 40 kHz, so the upper octave of rat hearing was not explored. In sound-exposed rats, the gain of the amplifier driving the speaker was increased to ensure that a sufficient dynamic range of sound level was available for studying neurons with elevated thresholds, especially for the random spectral shape (RSS) stimuli. Because of this and also because of variations in speaker distance and placement, the sound level at the peak of the mean curve in Figure 1A varied from 96 to 118 dB SPL across experiments. To show the variation in calibration shape, the mean SPL from 1 to 5 kHz was subtracted from each calibration and the mean and standard deviation of the resulting normalized calibrations computed. The green curves show the mean plus and minus one standard deviation at each frequency.

Data were obtained from 63 neurons in control and 102 neurons in sound-exposed rats. Data from one additional animal were excluded (10 neurons) because of uncertainties about the sound exposure and calibration in that animal. This had no effect on the results. All recordings were from well-isolated single neurons detected with a Schmitt trigger. The criteria for a single neuron were the following: (1) a constant action potential shape with good signal/noise ratio and no sudden changes in shape or amplitude, (2) a well-defined refractory period of one to several ms, and (3) fixed properties throughout the recording period. When a neuron was isolated, its best frequency (BF) was determined by finding the frequency to which the neuron was most responsive at low sound levels and the threshold was estimated to be the lowest sound level at which reliable responses appeared at BF in a rate-level function (200 ms BF tones, presented 1/s, over a 100 dB range in 1 dB steps of sound level).

A response map was constructed by recording responses to 200 ms tones (presented 1/s) logarithmically spaced in frequency across a (usually) 4-octave range containing BF. This process was repeated at 4–10 attenuations from a few

Fig. 1. **A** The acoustic calibration measured in free-field with a microphone in front of the intact pinna. *Black* the average calibration across 24 experiments; *green* ± 1 SD after eliminating variations in overall sound level from animal to animal due to changes in amplifier gain or speaker distance (see text). **B** Spectra of three (out of 212) RSS stimuli. Each step (or bin) in these stair plots contains eight equal-amplitude tones with frequencies evenly logarithmically spaced at 1/64 octave, giving one eighth octave wide bins. The amplitudes of each bin were set independently to produce a range of spectral shapes. The frequency scale of this plot is appropriate for a sampling rate of 168 kHz, which would be used for a neuron with best frequency (BF) 10 kHz. Note that the ordinates of parts A and B have the same dB scale, i.e., 20 dB occupies the same length on both scales. **C** Discharge rates during 300 ms presentations of RSS stimuli for one case. Rates for the first 100 (out of 212) stimuli are shown in blue. The *black dashed line* shows spontaneous rates and the *red dots* are the responses to 4 of the 7 all-zero-dB stimuli. **D** First-order (*top*) and second-order (*bottom*) filters derived from the rates shown in C. The *lines* are the mean weights and the *colored bands* are the SEMs. Only the two most important second-order filters are shown (*blue and red lines*) and compared to the first-order filter (*black dashed line*), after normalization of the latter to make the amplitudes equal. The BF of the neuron was 20 kHz. As is typical, the second-order filters may not be centered on BF, as for the red filter in this example.

dB above threshold to 60–80 dB above threshold. Response maps are shown in “Results” (Figs. 2 and 4) as plots of average discharge rate during the

tone versus frequency at constant attenuation across a range of sound levels. Spontaneous discharge rates for response maps were computed from the last half of the 800 ms interstimulus interval. From the response maps, spontaneous rates, and rate-level functions, neurons were classified according to the scheme used previously in DCN (Shofner and Young 1985), described in “Results.”

Finally, responses to RSS stimuli were obtained to characterize the spectral representations and the degree of nonlinearity of the responses (Young and Calhoun 2005; Yu and Young 2013). Briefly, the stimuli consisted of a sum of tones with random phase and frequencies logarithmically spaced at 1/64 octave. Each successive group of eight tones had the same amplitude and formed a frequency bin in the analysis (the stair steps in Fig. 1B); in some experiments following acoustic trauma, bins were 16 tones wide because of the reduced frequency resolution and broad frequency response ranges of those neurons. The amplitudes of tones in a bin were drawn from a Gaussian distribution with mean 0 and standard deviation 12 dB. Three examples of spectra are shown in Figure 1B; these contain 40 bins of varying amplitude over 5 octaves. The stimulus set consists

of 212 such stimuli and was presented as 300 ms bursts, once per second, with a single repetition of each stimulus. The reference level of the stimuli (0 dB in Fig. 1B) is varied to vary the overall sound level. RSS stimuli were presented in 10 dB steps over a range of levels covering as much as 80 dB. Seven of the 212 stimuli have 0 dB amplitudes in all bins (“all zero-dB” stimuli below). The RSS analysis can be thought of as measuring the responses to deviations of the stimulus spectrum from this all-zero-dB reference spectrum.

Changing the sampling rate of the stimulus slides the spectrum along the frequency axis, without changing its shape on a log-frequency abscissa. This property allowed the sampling rates of the RSS stimuli to be set so that the BF of the neuron was near two thirds of the total (log) frequency range of the stimulus, as for 10 kHz in Figure 1B. The two thirds centering was done because of the asymmetry of tuning curves; it allows approximately equal sampling of responses below and above BF.

Computation of Weight Models from RSS Stimuli

The RSS data were used to analyze complex stimulus processing using a model of stimulus-

Fig. 2. A–D Summary of the response characteristics of four neuron types in DCN. In each part, the *left plot* shows rate versus sound level for 200 ms bursts of BF tones (*light lines*) and broadband noise (*bold lines*). Spontaneous activity for the last half of the 800 ms interstimulus interval is shown *dashed*. The abscissa is in dB SPL for the tones and the noise rate function is aligned at the same attenuations as the tones (the noise had bandwidth 50 kHz and a spectral level 60 dB below the tone level). Plots are smoothed with a three-point triangular filter. The *right plot* shows a response map which is a plot of discharge rate versus frequency across a range of sound levels,

usually spaced at 10 dB. These are for 200 ms tone bursts. The sound levels are given at right as dB SPL at the BF. Of course, the sound level varies with frequency as in Figure 1A. The *red line* is the BF, labeled at the top. In the response map plots, the average rate during the tone is shown by the *solid lines*, which may be colored *blue* or *gray*, and the spontaneous rate by the *dashed lines*. Excitatory responses are *gray* and inhibitory responses are *blue*. These regions are meant only as general guidance and are assigned by eye based on contiguous sequences of frequencies with rates above or below spontaneous rate.

response relationships fit to the responses to RSS stimuli (Yu and Young 2013). Figure 1C shows the discharge rate versus stimulus number for the first 100 stimuli of an RSS set. Figure 1D shows the first-order and second-order filters that comprise the model, computed from the rates in Figure 1C. The filters were computed using the following weight function model:

$$r_j = R_0 + \vec{w}^T \vec{s}_j + \vec{s}_j^T \mathbf{M} \vec{s}_j. \quad (1)$$

r_j is the average rate in response to the j th RSS stimulus, whose spectrum is the vector $\vec{s}_j$ of dB values at different bin frequencies (Fig. 1B). $\vec{w}$ is a vector of weights, with units spikes/(s dB), at the corresponding frequencies. The dot product $\vec{w}^T \vec{s}_j$ represents a weighted summation of the dB values of the stimulus with weights that vary with frequency. The weights $\vec{w}$ thus represent the first-order tuning of the neuron (Fig. 1D, “1st-order”). Generally, the weight is maximum at BF, as in this example. Positive weights represent excitatory effects of the corresponding frequency and negative weights are inhibitory. The term $\vec{s}_j^T \mathbf{M} \vec{s}_j$ represents the second-order effects of stimulus frequency, composed of a sum of terms like $m_{kl}s_j(k)s_j(l)$, where m_{kl} is an element of the matrix $\mathbf{M}$. Each term represents the interaction of two frequencies (k and l) in determining the response of the neuron to the j th stimulus; the sum also includes terms like $m_{kk}s_j(k)^2$, a quadratic in the k th frequency. The constant value R_0 is the rate in response to the all-zero-dB stimuli (not the spontaneous rate).

The weight function model provides a description of the tuning of the neuron, including the frequencies at which it shows excitatory and inhibitory responses, which correspond to the filters’ passbands. The model also provides a measure of the linearity of the neuron, meaning how accurately the responses can be described by a low-order model like Figure 1. For neurons in sound-exposed rats, it will be shown below that the model provides a measure of the degree of sensitivity of the neuron to spectral shape, as opposed to overall sound level.

Although both first- and second-order components of Eq. 1 were computed for all cases, the results shown in this paper focus on the first-order terms. Details of the second-order terms are described in a previous paper (Yu and Young 2013). Briefly, second-order terms can be interpreted as a summation of squares of the outputs of a number of first-order filters, like those shown in the bottom half of Figure 1D. Often these second-order filters can account for a significant fraction of the responses of the neuron (up to 40 % of the variance).

The model of Eq. 1 is a linear function of the unknown parameters R_0 , $\vec{w}$, and $\mathbf{M}$. Thus, 205 equations of the form of Eq. 1 can be written (leaving out the all-zero-dB stimuli), using the discharge rates r_j measured in an experiment. The equations are solved for the unknown parameters using either the method of normal equations or singular-value decomposition (Press et al. 2007, chapter 15), both of which minimize the mean square error between the actual discharge rates and those predicted by the model. The accuracy of the model is given by the fraction of variance fv (or coefficient of determination)

$$\text{fv} = 1 - \frac{\sum_j (r_j - r_{mj})^2}{\sum_j (\hat{r}_j - \bar{r})^2}, \quad (2)$$

where r_j are the data values, r_{mj} are the estimated rates computed from the model, and $\bar{r}$ is the mean value of the data. The fv is one for a perfect fit, zero if the model predicts the data no better than the mean rate, and can be negative for very bad fits, usually involving significant constant errors (errors in average rate).

In fitting the model, one data point was left out and the model fit to the remaining (204) points. The accuracy of prediction of the left-out point is then a measure of accuracy of the model. This procedure is repeated, leaving out and predicting each data point in turn. Prediction is used because a large model like Eq. 1 substantially overfits the data, meaning that random noise in the data is fit by the model. Prediction tests the model with different noise (the noise of the left-out point) and thus provides a limit on overfitting.

To determine the number of parameters (i.e., the dimensions of $\vec{w}$ and $\mathbf{M}$), a brute force method was used in which parameters were added, beginning at BF. The parameter space was searched from 1 to the maximum number of parameters and the parameter set that maximized fv found. Empirically, the prediction performance improves (larger fv) until the point at which adding parameters mainly overfits the data, leading to a decrease in prediction performance. The values of $\vec{w}$ and $\mathbf{M}$ at the maximum are the ones used for further analysis.

The multiple fits to the data set described above yields 205 models, each estimated from a slightly different set of data. The final model is the mean of all the individual fits. The SEM of the parameter values (as in Fig. 1D) was calculated as $(n-1)\sigma_p/\sqrt{n}$, where n is the number of data points (205) and σ_p is

the standard deviation of the 205 weight estimates (Eq. 10.9 in Efron and Tibshirani 1993).

Usually, the model was fit to data obtained at one sound level only (i.e., the 212 RSS stimuli presented once apiece at the same attenuator setting). However, the model can be fit to data at multiple sound levels, e.g., 212 stimuli repeated at three different attenuator settings separated by 10 dB. In doing so, the stimulus vectors $\vec{s}_j$ are corrected for the different sound levels, using the 0-dB level of the lowest sound level case as the reference for the whole data set. Fitting responses to multiple sound levels were useful in modeling the responses of abnormal neurons in sound-exposed animals. As explained below in “Results,” multi-level fitting aids in understanding the properties of these neurons.

Statistics

Statistical testing was usually done with the rank-sum test for equality of the medians. *P* values are given for a two-sided test. In some cases, the chi-square statistic for contingency tables was used, again with two-sided *P*. For the data in Figure 5, multiple regression with main and interaction terms was used. For computation of weights from responses to RSS stimuli, the SEMs of the weight estimates are computed as described in a previous paragraph. Differences are considered to be not significant (NS) for $P > 0.1$, two-sided.

RESULTS

DCN Response Types in Rat

Responses to sound of DCN neurons have been characterized based on the distribution of excitatory and inhibitory responses across both frequency and sound level, as displayed in response maps (Evans and Nelson 1973; Young and Brownell 1976), and on the basis of temporal patterns of responses to short BF tone bursts (Godfrey et al. 1975; Rhode and Kettner 1987; Zhou et al. 2015). Because the response map approach relates responses of neurons to presumed anatomical neuron types as well as to the underlying inhibitory circuits, that approach is used here.

The organization of response maps is the same in rat as in other species (Young and Davis 2001; Caspary et al. 2005; Finlayson and Kaltenbach 2009; Zhou et al. 2012). Figure 2 shows examples of the four most common DCN response types as seen in control rats; these form a basis for the analysis of neurons after sound exposure. For each type, there are rate-versus-sound-level plots for BF tones and broadband noise (at left) and a response map showing rate plotted versus frequency at a sequence of sound levels (at right). For reference in later sections, the four types are briefly described below.

Type I/III and type III neurons (Fig. 2A, C) have a V-shaped excitatory response area (gray) centered at BF (red line). Type III neurons (Fig. 2C) are spontaneously active and show inhibitory responses (blue) at frequencies below and above the excitatory area, but inhibition is not seen in type I/III neurons. Both type I/III and III neurons respond strongly to BF tones and broadband noise, usually giving monotonic rate-level functions or functions with only small non-monotonicities.

Type II neurons (Fig. 2B) have low rates of spontaneous activity (< 2.5 /s), V-shaped excitatory areas centered on BF (Fig. 2B, right), and a characteristic non-monotonic rate-level function for BF tones. Most important, they give weak responses to broadband noise, compared to BF tones (Fig. 2B, left). Previous evidence shows that type II neurons are recorded from a glycinergic inhibitory interneuron (the vertical or tuberculoventral cell; Saint Marie et al. 1991; Kolston et al. 1992) which is responsible for much of the inhibitory response of type IV neurons (Voigt and Young 1990; Young 1980; Spirou et al. 1999; Rhode 1999; Zhou et al. 2012).

Type IV neurons have a large inhibitory response area (Fig. 2D, right) which includes BF. At the lowest sound level, type IV response maps have a small excitatory area centered on BF. These neurons have a characteristic rate-level function for BF tones (Fig. 2D, left) which is strongly non-monotonic. Their rate-level functions to noise are often monotonic, or at least excitatory at all sound levels above threshold, although this varies, as in the example in Figure 2D.

It is likely that types III and IV are recorded from DCN principal cells, both fusiform and giant cells (Young 1980; Rhode et al. 1983; Zhou et al. 2012). Typically, neurons of both types are mixed together in DCN recordings, and intermediate neurons, called type IV-T, are seen with weaker inhibition at BF (rate drops below half the maximum rate but not below spontaneous rate). Types III, IV-T, and IV form a continuum, probably varying in the strength of the inhibitory input received from type II neurons, as suggested by pharmacological manipulations that can convert neurons from one type to the other: pentobarbital converts IV to III (Evans and Nelson 1973; Young and Brownell 1976), bicuculline converts III to IV (Davis and Young 2000), and strychnine converts IV to III (Caspary et al. 1987; Davis and Young 2000). The focus of the analysis below is on these three neuron types, called *principal cell types* below.

Acoustic Trauma, Thresholds, and Spontaneous Activity

Following acoustic trauma and a variable period of recovery, single-neuron recordings were done in the DCN. The sound exposure used here produced a high-

frequency hearing loss of 40–60 dB as judged by ABR thresholds. Figure 3A shows examples of the ABR and single-neuron thresholds in two individual rats. The gray line shows the median ABR threshold in all control rats, and the blue lines are the ABR thresholds for these two rats. Thresholds for single neurons are shown by the symbols which are coded by response type, defined in the legend. Green symbols show neurons with responses of the types seen in control rats (the types in Fig. 2). Red symbols show responses that are seen only following acoustic trauma; these types, called “abnormal” in the rest of the paper, are defined in the next section and Figure 4.

Figure 3B shows thresholds of neurons from all of the sound-exposed rats. The frequency of the transition from roughly normal thresholds at low frequencies to shifted thresholds at high frequencies varied between rats. To make data from different rats comparable, the frequencies on the abscissa in Figure 3B are expressed in octaves relative to the *edge frequency*. The edge is defined as the halfway point of the transition from low to high ABR thresholds. The edge was found by averaging ABR thresholds in the low- and high-frequency regions where threshold is roughly constant, and then placing the edge at the frequency where threshold is halfway between these two average values. Edge frequencies are shown by the blue squares in Figure 3A; they varied from 6.5 to 30.2 kHz, median 11.8 kHz.

Generally, single-neuron thresholds were at or below the median ABR threshold (blue line in

Fig. 3B) for neurons with normal properties (green points) but could be below or above the ABR threshold in neurons showing abnormal properties (red points). Note that abnormal response properties are not confined to BFs with substantial ABR threshold shift, but rather extend to BFs 1–2 octaves below the edge frequency. These results are similar to the threshold distributions in cat DCN following similar acoustic trauma (Ma and Young 2006).

The principal cell response types were spontaneously active (median 28.6 /s, N=47 in control experiments) and spontaneous rates did not differ by response type. Following acoustic trauma, these neuron types remained spontaneously active (median 32.1 /s, N=43, NS compared to control). The abnormal response types (A, B, and C) were also spontaneously active, but at a lower rate (median 14.3 /s N=30, $P=0.016$ compared to control neurons), and several (7/30) had no spontaneous activity. The presence of spontaneous activity is important here because the response types shown in Figures 2 and 4 are defined based on the presence of inhibitory response areas, which are demonstrated by inhibition of spontaneous activity.

Abnormal Response Types after Acoustic Trauma

Response maps of the abnormal responses observed in DCN after acoustic trauma are shown in Figure 4. The largest change following acoustic trauma is the appearance of response maps with small or no inhibitory area and broadband excitatory areas (types

Fig. 3. Threshold shifts caused by sound exposure. **A** Two examples of data from individual animals. The gray line is the median ABR threshold in control animals, and the blue line is the ABR threshold in each animal. The blue square is the edge frequency (see text). The data points are thresholds at BF for individual neurons. Response types are given in the legend; red symbols are “abnormal” response types, defined in Figure 4. Exposure conditions: 114 dB for 1 h (top) and 116.5 dB for 2 h (bottom). **B** Data from the sound-

exposed animals (N=11), plotted as threshold (*ordinate*) versus frequency (*abscissa*). Points are single-neuron thresholds. Frequency is expressed in octaves relative to the edge frequency of the ABR threshold plot in the same animal. The blue line shows the median ABR threshold, after alignment on the edge frequency, and the gray region shows the range of individual ABR threshold functions. The light blue box shows the range of normal ABR thresholds. Dashed lines at ± 1 octave are shown to identify the edge region.

Fig. 4. Response maps from acoustic trauma animals showing three abnormal types (A, B, C). Plot conventions as in Figure 2. Response types are labeled above each response map. **A, B** Neurons with broad abnormal receptive fields and no inhibitory regions. The red curves in **A** show the median excitatory region in a normal type III neuron with a threshold at the median value (22 dB in exposed rats). Type B neurons have two apparent centers of frequency sensitivity

(vertical purple lines in **B**). **C, D** Neurons classified as type III and IV, despite the unusual features in the response maps, including two apparent responsive regions of the map in **C**. **E** Type C neuron with abnormal, primarily inhibitory, responses. The circled “e”s at the top of each response map show the edge frequency of the ABR from the same rat, as in Figure 3A.

A and B, Fig. 4A, B). Type A maps have only one excitatory area and BF, whereas type B maps have two excitatory regions separated by an area of no response (e.g., 3.5 and 6.8 kHz in Fig. 4B). A and B neurons are not observed in control rats but are common (17 and 8 %, respectively, Table 1) after acoustic trauma. The broadband excitatory regions resemble the tuning curves of auditory nerve fibers following acoustic trauma (Liberman and Dodds 1984; Miller et al. 1997). For comparison with tuning in unexposed animals, the red lines in Figure 4A show the median boundaries of the excitatory regions of type III neurons in control rats (obtained by aligning the type III response maps at BF threshold and then computing the medians of the low- and high-frequency edges of the excitatory area). The high-frequency edge (at about 31 kHz) is similar to that of type A and B neurons, but the low-frequency edge (at about 24 kHz) is much sharper in control neurons.

The edge frequencies of the animals in which these neurons were recorded are shown in Figure 4 by the circled “e”s. BFs of type A neurons were either below or above the edge (Fig. 3). However, in all B neurons (8/8), the lower tuned region was below the edge frequency and the upper region was at or above the

edge frequency (6.5 kHz in Fig. 4B). The lower tuned region of type B neurons was taken as the BF, meaning the region with responses at the lowest sound level.

Other neurons in exposed rats are recognizable as one of the principal cell types. The type III example in Figure 4C has two apparent BFs but is otherwise organized similarly to normal type III neurons. The type IV example in Figure 4D has a large, low-threshold inhibitory area at low frequencies (<7 kHz) that accompanies a rather typical type IV

Table 1		
Fraction of response types in control and sound-exposed rats		
Response type	Control	Sound-exposed
I/III	11 %	4 %
II	9 %	7 %
III	51 %	27 %
IV	19 %	13 %
IV-T	10 %	11 %
A		17 %
B		8 %
C		10 %
Unclassified		3 %
Total number	63	102

response map centered at 13.7 kHz. Large inhibitory areas were sometimes encountered in exposed rats. In some cases, called type C, the response map consisted largely of an inhibitory area (as in Fig. 4E) and the threshold for inhibition was below the threshold for excitatory responses at any frequency. In these neurons, the inhibitory BF, meaning the frequency at which inhibitory responses are observed at the lowest sound level, is at or below the edge frequency in all cases (9/9; see Fig. 3B). A few neurons (3 %) in exposed rats fit none of these patterns and remain unclassified.

As mentioned above, the thresholds of abnormal response types tend to be higher than those of normal types (Fig. 3B). Because thresholds for neurons of the three principal cell types did not differ, one from the other, either before or after acoustic trauma, the three types were combined in the following. Within the exposed rat population, the median thresholds are 22.7 dB for principal cells of normal response types (III, IV, and IV-T) and 43.0 dB for abnormal response types (A, B, C), where these thresholds are calculated relative to the lowest thresholds in normal rats at the same BFs (medians differ at $P < 0.001$, ranksum). To correct for the effect of cochlear damage on threshold at high BFs, a second analysis was done which compared the neuron thresholds in exposed animals to the median ABR threshold at the same frequency. Again, the abnormal neurons have a significantly greater probability of having thresholds above the ABR threshold (42 % for abnormal versus 14 % for control; $\chi^2 = 7.6$, 1 *df*, $P = 0.006$).

The prevalence of neurons of various types is summarized in Table 1. In sound-exposed rats, the abnormal response types A, B, and C and the unclassified cases account for 38 % of the neurons. The fractions of all the normal response types decrease in sound-exposed rats, but the decrease is largest for the type I/III and III neurons, suggesting

that many of the abnormal response types are disordered neurons originally of these types.

The recovery time between exposure and recording varied significantly in the population of exposed rats (from 103 to 376 days). To show the effect of recovery time variation, we computed the correlation between (1) the fraction of abnormal neurons (types A, B, C) in the population, (2) the number of days from exposure to recording, and (3) the mean ABR threshold above the edge. There is a weak tendency toward more abnormal neurons in rats with a longer recovery time and larger ABR threshold shift (Fig. 5A, B). However, the effects are not statistically significant by multiple regression. Also, there was no correlation between the threshold shift and the number of days of recovery (Fig. 5C; $r = 0.32$, NS).

Strength of Excitation and Inhibition

The data in Figure 3B and Table 1 are somewhat contradictory in that the prevalence of neuron types with strong inhibition (types IV and IV-T) is not reduced much overall by acoustic trauma (Table 1: types IV and IV-T are 29 and 26 % of neurons in control and exposed rats), whereas the number of neurons with significant inhibition is clearly smaller at BFs above the edge of the threshold curve (Fig. 3B, most such neurons are type III or type A). To further explore the question of inhibition in neurons from control and exposed rats, the relative strength of excitation and inhibition across frequency was determined. The measure used was the EI index defined as

$$EI = \frac{SE - SI}{SE + SI}, \quad (3)$$

where SE and SI are the sums across frequency of the excitatory and inhibitory responses for each sound

Fig. 5. Abnormal response types tend to be more common with larger threshold shifts and a longer recovery time. Shown are the fractions of abnormal neurons in the population recorded in each animal, plotted against: **A** The number of days from sound exposure to single-neuron recording. **Blue symbols** are all neurons in exposed animals; **red symbols** are from only those neurons with BFs in and above the edge frequency region. The **lines** show linear regressions. **B**

The mean ABR threshold shift at frequencies above the edge. **C** There is no significant correlation between mean ABR threshold shift and days expose to record. Multiple regression of fraction abnormal on days-expose-to-record and ABR threshold was NS for both main effects and interactions. Note that the ABR threshold could not be estimated in two experiments.

level in the response map, as illustrated by the gray and blue areas in Figure 6A. Because the frequency axis is logarithmic, the calculation actually reflects integrating over equal steps of log frequency. The EI index in Eq. 3 varies from -1 (strictly inhibition) to $+1$ (strictly excitation). Note that there is no attempt to define excitatory and inhibitory regions for this calculation, as in a response map; nor is there an attempt to limit the calculation to frequency ranges with significant responses. The random rate fluctuations around spontaneous rate that occur outside a neuron's response area produce a small noise and bias in the measures of SE and SI, which causes some irregularities in responses at low sound levels.

Figure 6B shows plots of EI index versus sound level for principal neurons in control rats. The type III neurons (red) have predominantly monotonic positive (excitatory) EI indices, as for the tone rate function in Figure 2C. However, the value of EI index

is often well below 1 for type III neurons because of the presence of inhibitory responses. Type IV neurons (blue) have positive EI at low sound levels and negative EI at high sound levels, like their BF rate-level functions (Fig. 2D). Type IV-T (gray) neurons are in between. The heavy solid lines show the medians of the EI index plots for the three neuron types.

In sound-exposed rats, principal cell types have similar EI index behavior (Fig. 6C, D); in these plots, neurons are separated by threshold, low (<25 dB SPL) in Figure 6C and high (≥ 25 dB SPL) in Figure 6D, to reveal effects of threshold shift. The data in Figure 6D are from neurons that receive inputs from the most damaged regions of the cochlea. In these plots, only the medians are shown as solid lines and the interquartile ranges occupied by the data are shown by the colored regions. For comparison, the median curves from control neurons are shown as dashed

Fig. 6. The relative strength of inhibition and excitation as measured by EI index (Eq. 3). **A** Plot of driven minus spontaneous rate versus log frequency, one line of a response map as in Figures 2 and 4. **SE** is the area of regions of positive rate change (gray) and **SI** is the area of regions of negative rate change (blue). EI index is -0.22 for this example. In actuality, the spontaneous rate varies across the plot (not shown), but it is only rate relative to spontaneous that is relevant. **B** EI index plotted versus sound level for principal neurons in control animals ($N=27$, 9, and 5 for types III, IV, and IV-T, respectively). Response type is indicated by color, defined in the legend. *Light lines* show data from individual neurons and *heavy lines* are medians in 10 dB bins. **C** Same as **B** for principal neurons in exposed animals ($N=11$, 9, and 9, respectively). These are neurons with smaller threshold shifts

(thr <25 dB SPL). *Shaded regions* show the interquartile range of the data, instead of individual neurons' rate functions. *Dashed lines* repeat the median lines from **B**. **D** Same as **C** except for exposed neurons with thresholds ≥ 25 dB SPL ($N=16$, 4, and 2, respectively). **E** EI index versus sound level for abnormal neuron types A, B, and C ($N=18$, 8, and 9 respectively). **F** Box plots summarizing the distributions of EI index (*ordinate*) for neurons from control and exposed animals; for each neuron, the median EI index over the sound levels 50–70 dB SPL was used. The data in parts **C** and **D** were combined here, i.e., ignoring threshold. The neuron types (III, IV, A, B, C) are given at the bottom along with animal treatment (control *cont* versus acoustic trauma *AT*). Ranksum statistical tests are summarized by the horizontal lines with significance: * $P<0.1$; ** $P<0.01$; *** $P<0.001$.

lines (repeated from Fig. 6B). The EI indices do not show a consistent movement toward excitation (EI index near +1), as would be expected if acoustic trauma simply weakened all inhibitory responses. Weakening of net inhibition is observed in type IV neurons (blue), but the opposite is seen in type III neurons (red) over most of the sound-level range.

Neurons with abnormal response types show the EI index values expected from their response maps (Fig. 6E). Type A and B neurons have indices near +1 at sound levels above threshold and type C neurons have negative EI indices, except at the highest sound level. Type C neurons typically had excitatory responses to tones at the highest sound levels, as in the example in Figure 4E.

The box plots in Figure 6F summarize the EI index data; for the purpose of this analysis, the median EI index was computed for sound levels from 50 to 70 dB SPL inclusive. All neuron groups have data at these levels, and the value of EI index in this range is usually typical of the suprathreshold behavior of a neuron. The first two (reddish) bars show type III neurons in control (labeled “III cont.”) and sound-exposed (“III AT”) rats. The median EI indices are not significantly different (0.67 and 0.56, respectively, $P=0.11$ ranksum). The EI indices for control type III neurons are significantly below those of type A neurons (“A AT,” median 0.95, $P=0.0015$), and also below type B neurons, but not significantly so (“B AT,” median 0.82, $P=0.14$). Thus, in neurons with predominantly excitatory responses, there is not a simple trend toward a decrease in inhibition following sound exposure. Instead, there are some neurons (type III) with more prominent inhibition after sound exposure and some neurons (types A and B) with less prominent inhibition. Of course, in making the comparison between type III and abnormal types, it is assumed that there is some relationship between them, such as that type A and B neurons represent pathological changes in type III responses induced by acoustic trauma, as suggested previously (Table 1).

The most sensitive measure of changes in inhibition occurs in type IV neurons, where inhibition dominates over much of the stimulus range, and so is not occluded by excitation, as occurs in type III neurons. Type IV neurons (blue bars) have significantly weaker inhibitory responses after sound exposure (median index -0.84 for control vs. -0.19 for exposed, $P<0.001$ ranksum) and the abnormal type C responses also show weaker inhibition (median -0.48 , different from control type IV, $P=0.005$ ranksum). Again, if it is assumed that type C responses are obtained from neurons that were type IV or IV-T before acoustic trauma, then the effect of trauma is a weakening of inhibition.

Responses to Complex (RSS) Stimuli

Neurons in DCN are sensitive to features of the stimulus spectra of sounds, such as notches or rising spectral edges and this sensitivity involves a balance of excitatory and inhibitory effects (Parsons et al. 2001; Reiss and Young 2005; Bandyopadhyay et al. 2007). Thus, the post-sound-exposure changes in receptive fields described above could change the functional properties of DCN neurons in important ways. To explore neurons' sensitivity to stimulus spectra, we used RSS stimuli (Fig. 1B).

Following acoustic trauma, the most dramatic changes in spectral sensitivity occurred in the abnormal neurons, in which selectivity for spectral features of the stimuli often was largely lost. An example is shown by the comparison in Figure 7. The response maps of a type III neuron (top row) and a type A neuron (bottom row) are shown in Figure 7A, D for reference. The middle column (Fig. 7B, E) shows comparisons of the stimulus spectra giving the 20 highest discharge rates (top plot in each pair) and the 20 lowest discharge rates (bottom plot) in response to the full complement of RSS stimuli. The gray lines show the spectra of the 20 stimuli, and the blue lines are averages of these. For the type III neuron (Fig. 7B), there is a clear signature in the spectra to which the neuron responds most strongly; these spectra have energy near the neuron's BF (7.4 kHz, the gray vertical line) and less energy at about 8.2 kHz. These features can be seen in the consistent variation of the individual spectra (gray) but are easier to see in the average. At frequencies further from BF, the mean spectrum fluctuates noisily, but there is no consistent pattern among the individual stimuli. The lowest rates are recorded in response to stimuli with the opposite spectral features (lower plot in Fig. 7B), namely little energy near BF with a peak of energy above BF (near 8.2 kHz). This feature is particularly clear in both the individual spectra (gray) and the average (blue).

The weight functions of the model fit to these data are consistent with the qualitative description of the previous paragraph. The first-order weights ($\vec{w}$ in Eq. 1) are shown in the inset at the top of Figure 7B. As expected from the stimuli, the weights are large and positive at the frequency where the best 20 stimuli have a peak in energy and the worst 20 have a valley. There is also a small region of negative weights above BF, an inhibitory area that corresponds to the peak of energy in the worst 20 stimuli.

Typical of type III neurons in DCN (and also VCN neurons and type I neurons in inferior colliculus; Yu and Young 2000, 2013), the neuron in the top row gave responses to spectral shapes that are accurately predicted by the weight function model (Fig. 7C). The predictions are based on the full model in Eq. 1, i.e., include both first-order and second-order terms. The f_v of the prediction is 0.73, which is typical of type III neurons, and shows a good sensitivity to the spectral

shape of the stimulus near the neuron's BF and a linear representation of that spectrum.

The type A neuron in Figure 7D–F shows different characteristics. First, there are no particular features in the top 20 and bottom 20 stimuli or their averages, except possibly a small broad peak near BF in the top 20 stimuli. The first-order weights in the inset at the top of Figure 7E show a broadly tuned characteristic with a peak near the BF (4.6 kHz) and an apparent second peak at 2.3 kHz. However, note that the amplitudes of these weights are very small, less than 0.1, more than an order of magnitude smaller than the peak weights in the type III neuron in Figure 7B. Thus, the type A neuron does not respond strongly to stimulus energy at any particular frequency.

In fact, the responses of the type A neuron seem to be driven by the overall stimulus level and not the spectral shape. This fact can be appreciated by

looking at the average sound level of the top 20 stimuli (near 40 dB) versus the level of the bottom 20 stimuli (near 20 dB). This ~20 dB difference is as large as possible, given the variation of the sound levels of the stimulus set used to obtain these data, which were the 212 stimuli in the RSS set presented three times at three different attenuator settings, separated by 10 dB. This neuron apparently responded most strongly to the stimuli with the highest overall level, and frequency-selective effects are weak if present at all. The example chosen for Figure 7B shows this effect of overall stimulus level to a much smaller degree, in that the average stimulus levels are about the same for the top and bottom 20 stimuli. This type III neuron responded mainly to spectral shape and not overall stimulus level. Other type III neurons show more response to the overall stimulus level, but importantly, almost all the responses to RSS stimuli

Fig. 7. Examples of responses to RSS stimuli, showing good spectral representation in a type III neuron and responses dominated by overall sound level in a type A neuron. **A, D** Response maps of two example neurons as in Figures 2 and 4. **B, E** Two plots showing the spectra of the 20 RSS stimuli giving the highest discharge rates (“top 20”) and the lowest discharge rates (“bottom 20”). The blue curves are the averages of the 20 spectra, and the vertical lines show the BFs of the neurons. Each RSS stimulus was presented three times at three attenuations spaced by 10 dB, for a total of 636 stimuli. The dB values on the ordinates are the sound levels of the stimuli relative to the threshold of the neuron for RSS stimuli. Thus, the two plots in B are on the same ordinate, but it is different from the two ordinates

in E. Note the consistent average stimulus features (blue lines) in B, comparable to the first-order weight function of this model (in the inset at top); by contrast, there is little or no feature in E. Importantly, the overall levels of the stimuli are ~20 dB higher for the top 20 compared to the bottom 20 stimuli in E. The horizontal gray lines are placed at the 0 dB level of the lowest of the three RSS sound levels. **C, F** Actual discharge rates produced by the RSS stimulus set (abscissa) versus the rate predicted by the weight function model (ordinate), computed as described in “Materials and Methods.” The full second-order model of Eq. 1 was used. The fv values show good prediction for the type III neuron (C) but not for the type A neuron (F).

in control rats (11/12) and 60 % of the responses in exposed rats (12/20) also show the good representation of spectral shape near BF ($fv > 0.6$).

The ability of the weight function model to predict responses to stimulus spectra is poor in the type A neuron, as shown in Figure 7F. The fv is only 0.37, and the model rate varies over a smaller range than the actual rates.

Population Data for Responses to Complex Stimuli

Population data on the quality of spectral representation measured with RSS responses are shown in Figures 8 and 9; Figure 8 shows model fit quality fv versus sound level. The results are summarized by the boxplots in Figure 8D, where fv values are computed as the median of the fv s at sound levels from 10 to 30 dB re RSS threshold (vertical dashed lines in Fig. 8A–C).

In control ears (Fig. 8A), prediction accuracy is high ($fv \sim 0.79$) in type III neurons (red) and smaller ($fv \sim 0.5$) in type IV and IV-T neurons (blue; types IV

and IV-T are combined for this analysis because the number of neurons is small and because their data appear to be similar). For both neuron types, fv does not vary much with sound level. Previous data have shown that type IV neurons are less linear than type III neurons, meaning that the RSS model does not predict responses as well (Yu and Young 2000). This difference is significant in the present data (median fv values 0.79 and 0.50, $P < 0.001$ ranksum).

In exposed ears (Fig. 8B), the behavior of fv is generally similar to control. The fv values are again higher in type III neurons compared to type IV/IV-T neurons (medians 0.64 and 0.42, $P = 0.006$). However, fv values are only slightly different between control and exposed ears in both neuron types (type III, medians 0.79 and 0.64, $P = 0.04$; type IV/IV-T, medians 0.50 and 0.42, NS). The major new feature in exposed ears is the appearance of abnormal response types (green in Fig. 8B, C). These neurons have substantially lower fv values, consistent with the poor quality of spectral representation discussed in Figure 7E, F; the differences between control and abnormal neurons are large and significant (type III versus abnor-

Fig. 8. Acoustic trauma reduces the accuracy of the spectral representation, judged by the quality of weight model fits to rate responses. **A** fv for model fits to data in control animals, plotted against sound level. Data are shown separately for type III ($N=8$) and types IV and IV-T together ($N=7$). The heavy lines are median values in 10 dB bins. **B** Same plot for type III ($N=9$), type IV plus IV-T ($N=12$), and abnormal types (A–C, $N=10$). Data for all thresholds are included; data in different threshold groups are not statistically different. **C** Same for abnormal neurons (types A, B, C, $N=4, 3, 3$). Green plots are repeated from **B** for fits at single sound levels and gold

plots are fits to multiple sound levels simultaneously; for the multi-level fits, only one data point is plotted for each neuron, at the highest sound level. The gold line is the population median as usual. **D** Box plots summarizing the distributions of fv in various neuron types (III, IV/IV-T, and abnormal) for control (cont) and exposed (AT) animals. The fv value for each neuron is its median value between 10 and 30 dB re threshold (between the vertical dashed lines in parts A, B, C). Ranksum statistical comparisons are summarized by the horizontal lines with significance: * $P < 0.1$; ** $P < 0.01$; *** $P < 0.001$.

mal medians 0.78 and 0.23, $P \ll 0.001$; type IV/IV-T versus abnormal medians 0.50 and 0.23, $P = 0.008$).

A major feature of the abnormal neurons is that the quality of the model prediction improves when the model is computed from data at several sound levels. A weight function model can be derived from responses to the RSS stimuli presented at one reference sound level, which is the condition for the data in Figure 8A, B. However, it is also possible to fit the weight model simultaneously to data from repetitions of the RSS stimuli at several attenuator settings. In doing so, the sound levels ($\vec{s}$ in Eq. 1) are adjusted to reflect the differences in attenuation. Fitting the model over multiple sound levels makes only a small difference in control neuron types (not shown) but improves the quality of the model, as judged by f_v , for abnormal neuron types. This point is demonstrated in Figure 8C, where the gold data points were computed using a model fit to all the sound levels available for a neuron and the green data points were computed with single-level data for the same neurons. The improvement is significant (medians 0.49 for gold and 0.23 for green, $P = 0.004$). Presumably, the improvement in the fit quality results from the wider range of sound levels in the data, so that a larger

fraction of the variance in the stimulus is attributable to overall level variation, as opposed to local variations in spectral shape. This result is further evidence for the hypothesis discussed in connection with Figure 7 that abnormal types are responding to the overall sound level of the stimuli over a wide frequency range, instead of a narrowband spectral shape in the vicinity of BF.

The magnitudes of the weights are shown in Figure 9 in the same format used for Figure 8. The most noticeable feature of Figure 9 is the large weights in some type III neurons in control rats (Fig. 9A red data points). The control type III weights are significantly larger than weights in types IV and IV-T neurons (medians of the maximum weight value across sound level are 5 and 1.2 spikes/(s dB), respectively, $P = 0.004$). This difference in weight amplitudes corresponds to the higher prediction quality in the type III neurons. Such a relationship (larger weights and higher prediction quality) is usually observed across different neuron types.

Acoustic trauma reduces the weight amplitudes of type III neurons substantially (Fig. 9B; medians 5.0 in control rats to 1.4 after acoustic trauma, $P = 0.006$). There is no significant effect of acoustic trauma on

Fig. 9. Acoustic trauma reduces the gain of the responses to RSS stimuli; same data as Figure 8. The plots show the Euclidian norm (or length) of the first-order weight vector $\|\vec{w}\|$ plotted against the sound level of the stimulus relative to RSS threshold. **A** Norm versus level for control neurons. Types IV and IV-T are lumped together because of similarity of data. **B** Same plot for neurons following acoustic trauma. **C** Same for abnormal neurons fit to each sound

level individually (green) and fit simultaneously to all sound levels (gold). **D** Box plots summarizing the distributions of weight norm in various neuron types (III, IV/IV-T, and abnormal) for control (cont) and exposed (AT) animals. Each neuron's norm value is the peak of the plot of norm vs sound level. Ranksum statistical comparisons are summarized by the horizontal lines with significance: * $P < 0.1$; ** $P < 0.01$; *** $P < 0.001$.

the weight amplitudes in type IV and IV-T neurons. However, abnormal types (Fig. 9C) have significantly reduced weights relative to both type III and IV/IV-T neurons (median 0.69, $P < 0.001$ compared to type III and $P = 0.09$ compared to type IV/IV-T). There is one abnormal neuron that is an exception to this statement, easily seen in Figure 9B, C.

Although computing weights from stimuli at several sound levels gives better prediction performance in abnormal neurons (Fig. 8C), it does not make the weights larger in amplitude (Fig. 9C, gold data points). In fact the shapes of first-order weight functions are not much changed by computing the model over multiple sound levels. Thus, the improvement in prediction performance noted in Figure 8C is not due to an improvement in either weight amplitudes or the weight function shape, strengthening the argument for a broadband non-selective mode of functioning in these neurons.

DISCUSSION

Effects of Acoustic Trauma

The post-exposure thresholds produced here are typical of results from narrowband exposures, which give a threshold shift at and surrounding the exposure frequency, accompanied by relatively normal thresholds at very low or very high frequencies (Liberman and Dodds 1984; Miller et al. 1997). In the present data, the recordings did not extend to high enough BFs to see the very high-frequency part of the threshold function. The median ABR threshold at low frequencies (below -0.5 octave relative to the edge frequency) returns to near normal thresholds but remains at the upper limit of control ABR thresholds (the blue box in Fig. 3B), suggesting that a small threshold shift, from 0 to 20 dB, exists at these frequencies. In Sprague-Dawley rats, there can be an age-related ABR threshold shift of ~ 10 dB at the age of our oldest rats when tested (18 months; Sanz-Fernández et al. 2015). Although this shift is small compared to the effects of noise exposure above the edge, it could account for some part of the low-frequency threshold shift and affect our other results as well.

Exposures like those used here produce a mixed lesion of inner and outer hair cells in the cochlea (Liberman and Dodds 1984). In addition, recent work shows that there is likely to be substantial damage to spiral ganglion neurons and their synapses with hair cells (Kujawa and Liberman 2009), with consequent disruption of synapses in the cochlear nucleus (Kim et al. 2004).

In the DCN, this acoustic trauma resulted in neurons with abnormal response maps (Fig. 4). Gen-

erally, the higher the threshold of a neuron, the more likely it was to have an abnormal response map; although this was a significant effect in individual neurons (Fig. 3B), it was not in the population average (Fig. 5). Surprisingly, Figure 3B shows that abnormal neurons are common at BFs well below the edge frequency of the exposure, which is well below the exposure frequency (median edge at 11.8 kHz, exposure at 16 kHz). A similar result was seen in cats (Ma and Young 2006). Thus, reorganization of responses in DCN neurons occurs both in regions with substantial cochlear threshold shift (and inferred hair cell damage) and regions where cochlear thresholds are near normal (where hair cell damage should be small). Presumably, these abnormal responses in regions with minimal threshold shift occur because auditory nerve fiber degeneration can occur in regions where the threshold shift is temporary, i.e., the hair cells recover from the exposure (Kujawa and Liberman 2009; Du et al. 2012; Tagoe et al. 2014).

Recently, a number of researchers have reported that spontaneous activity is elevated in DCN following sound exposures of varying severity (e.g., Zhang and Kaltenbach 1998; Brozoski et al. 2002; Finlayson and Kaltenbach 2009; Middleton et al. 2011; Dehmel et al. 2012). Elevated spontaneous activity was not present in the data of this study, in agreement with previous results in cat DCN (Ma and Young 2006) and in the likely targets of DCN projections in the rat inferior colliculus (type O neurons; Ropp et al. 2014). The reasons for the difference between our results on hyperactivity and those of others are not clear. Most of the papers reporting hyperactivity used rodents (rats, guinea pigs, hamsters) anesthetized for recording with ketamine/xylazine, ruling out a species-specific effect or a difference in anesthetic (for example, the possible interaction of NMDA channels and hyperactivity; Brozoski et al. 2013). The difference in data is likely due to differences in methods, either in the details of the exposure protocol or the neuron recording procedures. One important difference is the use of single-neuron recording here versus multineuron recording in many, but not all the papers reporting hyperactivity. Another consideration is the state of inhibition in the preparations. Spontaneous activity can only be affected by inhibition if the inhibitory neurons are spontaneously active. In the cochlear nucleus, two inhibitory neuron types, the vertical (type II) cells and D-stellate neurons in VCN are not spontaneously active, but a third type, cartwheel cells, is. Thus, variation in the state of cartwheel cell activity among studies might be responsible for variable results on spontaneous activity. The granule cell-associated superficial circuits in DCN, which activate the cartwheel cells, show substantial activity-dependent plasticity, especially after acoustic

trauma (Tzounopoulos et al. 2007; Middleton et al. 2011; Pilati et al. 2012; Kou et al. 2013). The state of inhibition from those circuits has been estimated from the strength of inhibitory responses to somatosensory stimuli (Shore et al. 2008; Dehmel et al. 2012) with results consistent with decreased cartwheel cell inhibition, a result that implies an increase in spontaneous activity. Because the degree and nature of plasticity in superficial DCN following acoustic trauma is likely to depend on contingencies like the nature of the sound environment or the degree of non-acoustic stimulation of the superficial DCN circuits during recovery, this plasticity could be a source of variability in DCN spontaneous activity.

Locations and Mechanisms of Type A, B, and C Abnormal Neurons

The distributions across frequency of the three types of abnormal neurons differ. Above the edge frequency, almost all abnormal neurons are type A (7/8, 88 %), whereas below the edge frequency, only 39 % (11/28) are. Type A neurons have elevated thresholds and broad tuning, resembling auditory nerve fibers in animals with similar threshold shifts (Liberman and Dodds 1984; Miller et al. 1997). In the absence of contrary evidence, the simplest explanation for type A responses is that they reflect excitatory inputs from such damaged auditory nerve fibers, along with a weakening or loss of inhibitory inputs. The loss of inhibition could reflect circuit reorganization or homeostatic effects, but it is interesting to note that type II neurons (DCN inhibitory interneurons) were rarely seen at frequencies above the edge in this study (1/7, Fig. 3B) or in a previous study in cat (1/6; Ma and Young 2006).

By contrast, type B neurons have BFs below the edge frequency (8/8), also observed in cats (Ma and Young 2006). Type B response maps are similar to type A response maps at frequencies below the edge, with the addition of a small excitatory region at higher frequencies, at or above the edge. Based on a previous analysis of such neurons (Kaltenbach et al. 1992), it seems that the low-frequency part of the type B response map reflects damaged auditory nerve inputs as for the type A response map. The higher frequency responses may reflect the remnant of the neuron's pre-trauma dominant BF inputs at frequencies above the edge, now threshold-shifted by the acoustic trauma.

Type C responses occur in neurons with BFs (including inhibitory BFs when the lowest-level responses are inhibitory as in Fig. 4E) at or just below the edge frequency (8/8); they are characterized by large inhibitory areas at the lowest sound levels to which the neuron responds. There is a range of such neurons, from the type III and type IV examples in

Figure 4C, D which have a low-threshold inhibitory area but preserve roughly normal response features at higher frequencies, to the predominantly inhibited type C neuron in Figure 4E. Type II neurons are present in the frequency region just below the edge, so it seems plausible that type C neurons are those with low-threshold inhibitory inputs from these type II neurons, but damaged excitatory (and perhaps also inhibitory) inputs at frequencies above the edge.

Lessening of Inhibition Varies with Response Type

Generally, inhibition weakens following trauma, with the one exception that type III neurons in Figure 6F have a wider distribution of EI indices after trauma, with a lower median. Otherwise, quantitative analysis of the balance of inhibition and excitation in tone-based response maps shows more excitation following acoustic trauma. First, two response types with no or very little inhibitory response appear (types A and B). One can speculate that these are former type III and I/III neurons (prior to trauma), based on the argument that those response types are most reduced in number following acoustic trauma (Table 1). These are predominantly excited neurons in normal animals, so a weakening of inhibitory inputs could be sufficient to mask or eliminate the inhibitory responses of these neurons. Second, predominantly inhibited response types have weaker inhibition following acoustic trauma. This trend can be seen from the medians of the EI indices of types IV and C in Figure 6C, which move toward excitation after trauma.

Weakening of inhibition in the DCN following acoustic trauma is expected from the previously reported trauma-induced loss of glycinergic receptors and associated molecules in DCN (Asako et al. 2005; Wang et al. 2009; Whiting et al. 2009) and from the weakening of glycinergic post-synaptic potentials in VCN (Xie and Manis 2013).

Representation of Complex Stimuli

In control rats, the DCN shows two types of information representation, with respect to spectral shape. The first is linear (type III neurons), in which the spectral content of the stimulus at frequencies near BF is accurately represented in a direct fashion by rate (e.g., higher rates for higher stimulus levels; Fig. 8A). The second channel is nonlinear in type IV and IV-T neurons. The mutual information between the stimulus and the neuron's discharge rate is as large for nonlinear neurons as for linear ones, like type III, but the representation in terms of rate may be indirect (e.g., either a rate increase or a decrease occurs for higher stimulus levels, but it does so reliably). Although the nonlinear type IV channel provides as

much information about the stimulus as does the linear channel (Young et al. 2005), the nonlinearity means that even the second-order weight model does not capture all the variance in rate responses to a stimulus (Nelken et al. 1997; Yu and Young 2000).

Importantly, the linear type III channel shows a high gain for spectral features (Fig. 9A), compared to other neuron types and auditory nerve fibers (which show a maximum weight ~ 2 spikes/(s dB); Young and Calhoun 2005). Acoustic trauma reduces the accuracy of the representation of spectral shape (Fig. 8D) only slightly in type III and IV/IV-T neurons, but it reduces the gain of the type III weight functions significantly (Fig. 9D).

A natural question is whether there is a connection between inhibition and the quality of the spectral representation of RSS stimuli. This question is best answered in the type III population, which is most numerous and has the highest f_v in control animals. There is a positive correlation between the EI index and f_v of model fits to RSS stimulus responses among type III neurons ($r=0.46$, $P=0.02$, $N=25$, including both control and post-exposure data). This effect occurs largely because the high EI (mostly excitatory), high f_v (linear rate representation) neurons in control rats change to broadly scattered EI values, including many with low f_v values, after acoustic trauma. This result seems to imply that stronger inhibition (lower EI) produces a less linear rate representation. Although this is consistent with the lack of linearity in strongly inhibited type IV and IV-T neurons in DCN (Nelken and Young 1997), the correlation depends mainly on the effects of trauma and so it may occur because of the disordered integration of excitation and inhibition following trauma, including such effects as broadened tuning bandwidths.

Because the linear channel provides the best representation of the spectra of stimuli, the decrease in gain in type III neurons (Fig. 9A, B) means a decrease in the clarity or signal-to-noise ratio in the representation of sound spectra. In addition, the largest effect of acoustic trauma is the appearance of a significant number of neurons of abnormal response types, where the representation of stimulus spectrum is poor and the neural responses represent mainly the overall sound level. If changes like those reported here are typical of the other auditory pathways (e.g., through the VCN), then these two effects would appear in a hearing-impaired listener as a deficit in discriminative ability for complex signals, like speech. Of course, this deficit would not be ameliorated by amplification.

Conclusion

The results here show a decrease in functional inhibition in DCN neurons that correlates with the

previously reported loss of inhibitory markers following acoustic trauma. At the same time, there is a disordering of the neural circuits by acoustic trauma which degrades the representation of the spectrum of the stimulus at suprathreshold levels, especially in the abnormal neurons and in the linear channel. The very low gain of the abnormal neurons for the spectral shape of the stimuli provides a substrate for hearing impairment resembling neuropathy, in that there is a clear signal for the presence of sound, but not one that allows discrimination of sounds based on spectrum.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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