

A Sensitive Period for the Impact of Hearing Loss on Auditory Perception

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Manipulations of the sensory environment typically induce greater changes to the developing nervous system than they do in adulthood. The relevance of these neural changes can be evaluated by examining the age-dependent effects of sensory experience on quantitative measures of perception. Here, we measured frequency modulation (FM) detection thresholds in adult gerbils and investigated whether diminished auditory experience during development or in adulthood influenced perceptual performance. Bilateral conductive hearing loss (CHL) of ≈ 30 dB was induced either at postnatal day 10 or after sexual maturation. All animals were then trained as adults to detect a 5 Hz FM embedded in a continuous 4 kHz tone. FM detection thresholds were defined as the minimum deviation from the carrier frequency that the animal could reliably detect. Normal-hearing animals displayed FM thresholds of 25 Hz. Inducing CHL, either in juvenile or adult animals, led to a deficit in FM detection. However, this deficit was greater for juvenile onset hearing loss (89 Hz) relative to adult onset hearing loss (64 Hz). The effects could not be attributed to sensation level, nor were they correlated with proxies for attention. The thresholds displayed by CHL animals were correlated with shallower psychometric function slopes, suggesting that hearing loss was associated with greater variance of the decision variable, consistent with increased internal noise. The results show that decreased auditory experience has a greater impact on perceptual skills when initiated at an early age and raises the possibility that altered development of CNS synapses may play a causative role.

Key words: critical period; deafness; frequency discrimination; temporal processing

Introduction

The influence of sensory experience on neural structure and function varies with age. Loss of peripheral sensory activity has a greater impact when it occurs during developmental sensitive periods. Interventions that restore activity (e.g., cochlear prostheses) during these epochs are associated with better recovery of neural function (Ponton and Eggermont, 2001; Keuroghlian and Knudsen, 2007; Espinosa and Stryker, 2012; Kral and Sharma, 2012). However, the onset and duration of sensitive periods during which neural function is vulnerable to sensory deprivation depends on the specific property (Hooks and Chen, 2007; de Villers-Sidani and Merzenich, 2011; Erzurumlu and Gaspar, 2012). Therefore, if neural-sensitive periods for sensory deprivation are a reliable proxy for perception, then behavioral measures should display a strong dependence on the deprivation age of onset. Here, we tested this principle by measuring perceptual performance in gerbils that were reared with hearing loss or that acquired the same hearing loss in adulthood.

Auditory perceptual deficits are commonly attributed to peripheral dysfunction because inner ear damage disrupts cochlear processing (Oxenham and Bacon, 2003). However, prolonged periods of conductive hearing loss (CHL) due to chronic otitis media may also induce perceptual deficits (Whitton and Polley, 2011). In fact, the central encoding of spatial location is profoundly altered by unilateral CHL and these functional changes can account for impaired perceptual abilities (Clements and Kelly, 1978; Knudsen et al., 1984a, 1984b; Wilmington et al., 1994; Moore et al., 1999; Parsons et al., 1999; King et al., 2000; Popescu and Polley, 2010). Furthermore, direct measures from auditory cortex demonstrate that CHL induced at the time of ear canal opening disrupts synapse function, but not when induced in adulthood (Takesian et al., 2012). Therefore, we investigated the perceptual consequence of bilateral CHL because this form of hearing loss produces air-conducted sound attenuation but does not raise bone-conducted thresholds, indicating no cochlear damage (Tucci et al., 1999).

To evaluate a sensitive period for perceptual maturation, we measured frequency modulation (FM) detection, a fundamental property of communication sounds, including speech (Singh and Theunissen, 2003). Because this percept matures slowly (Banai et al., 2011), we reasoned that it would remain vulnerable to deprivation during development. Indeed, children and adults with sensorineural hearing loss display poorer FM detection thresholds (Moore and Skrodzka, 2002; Buss et al., 2004; Halliday and Bishop, 2006). Because there is evidence both for neural sensitive periods and neural consequences of adult-onset hearing loss

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(Syka, 2002; de Villiers-Sidani and Merzenich, 2011; Kral and Sharma, 2012), we controlled for the onset age, magnitude, and duration of CHL. Our findings reveal that FM detection thresholds were impaired by hearing loss in both young and adult animals, but the effect was more severe when hearing loss onset occurred during development.

Materials and Methods

Animals and groups. Behavioral data were obtained from adult Mongolian gerbils (*Meriones unguiculatus*) divided into three treatment groups: normal-hearing gerbils (control adult, $n = 16$ of either sex), gerbils with CHL induced in adulthood (adult CHL, $n = 23$ of either sex), and gerbils with CHL induced before ear canal opening (postnatal day 10 [P10] CHL, $n = 17$ of either sex). All groups were trained and tested on the behavioral task as adults ($\geq P70$). Two adult CHL and one P10 CHL gerbil were excluded from the study because they failed to learn the task after 10 sessions. An additional adult CHL was removed from the study after it developed an infection. All animals were weaned at the same age, housed in our animal colony, and trained and tested under the same conditions.

Three cohorts comprised the P10 CHL group and were deprived before ear canal opening. Two of these cohorts were tested as young adults at $\approx P90$ (i.e., after 80 d of deprivation). To determine whether duration of deprivation has an impact on FM depth perception, one cohort was tested after 1 year of CHL. Because there was no statistically significant difference in the variance of log-transformed FM thresholds (Levene's test, $p = 0.36$, $df = 1$, $F = 0.89$) or mean FM threshold (Welch's two-sample t test, $t = 0.24$, $df = 13.24$, $p = 0.81$) between those tested as young adults and those tested after 1 year of sensory deprivation, we pooled the data for all subsequent analyses.

The initial experiment for testing the effect of acute sensory deprivation on FM detection in adults (i.e., the adult CHL group) used six gerbils of either sex that had prior experience on the task as normal-hearing adults. The second and third cohorts of this group (six gerbils each of either sex) had no prior experience at the time of training and testing. In the first three cohorts, all animals were tested after 14–30 d of sensory deprivation. To determine whether duration of deprivation has an impact on FM depth perception, an additional adult cohort (five gerbils of either sex) was tested after 80 d of sensory deprivation, similar to the P10 CHL group (see Fig. 2C, orange diamonds). We found no statistically significant difference in the variance of log-transformed FM thresholds (Bartlett's test, $T = 2.46$, $p = 0.29$) or mean FM threshold (one-way ANOVA, $F = 1.15$, $p = 0.33$) between these three subgroups (i.e., trained adult CHL, acute adult CHL, and aged acute CHL). Therefore, we treated all adult-onset CHL animals as a single group for all subsequent analyses.

Surgery for CHL. Bilateral CHL was induced before ear canal opening (P10) for the P10 group or after sexual maturation (P83) for the adult CHL group. Short-term surgical analgesia was induced using methoxyflurane (Medical Developments International) and the malleus removed through a perforation in the tympanic membrane (Tucci et al., 1999; Rosen et al., 2012). This procedure induces an attenuation of ≈ 55 dB at 4 kHz, as assessed by auditory brainstem response (Tucci et al., 1999; Rosen et al., 2012). However, behavioral measures obtained in the present study indicate an attenuation of ≈ 30 dB at 4 kHz (see Results).

Behavioral assessment. Animals were placed on controlled water access and trained to drink from a lick spout in the testing cage. Figure 1 illustrates the stimulus waveform and trial structure of the behavioral procedure. All animals were trained to detect a 1 s, 5 Hz sinusoidal FM embedded in a continuous 4 kHz tone carrier at 45 dB SPL (normal-hearing controls) or 95 dB SPL (P10 CHL and adult CHL groups) to compensate for the elevated thresholds. Task difficulty was adjusted by controlling the maximum deviation of the modulation (FM depth) from the carrier frequency (Fig. 1). The FM cue was followed by a mild aversive stimulus (300 ms electrical shock) delivered via the metal lick spout (Heffner and Heffner, 1995; Kelly et al., 2006; Sarro and Sanes, 2010; Rosen et al., 2012). Within a few sessions, animals learned to avoid the shock by breaking contact with the lick spout when they detected the FM

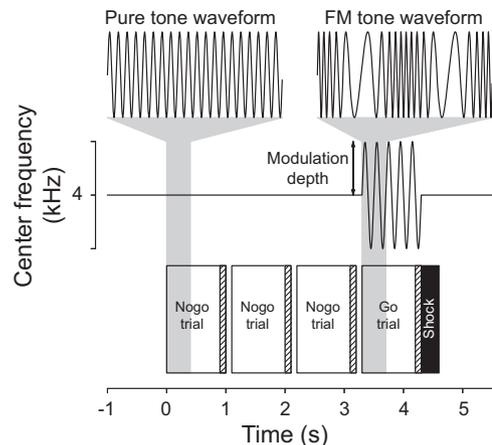


Figure 1. Overview of FM detection task. The target (a sinusoidally frequency modulated tone) is embedded in a continuous 4 kHz carrier at a rate of 5 Hz. Task difficulty was modulated by adjusting the maximum frequency deviation from 4 kHz (arrow, modulation depth). Examples of the fine structure for a pure and FM tone waveform are shown above the center frequency plot. Trials, each lasting 1 s, were presented at a rate of $\sim 1/s$ while the animal was drinking from the water spout. Three to five no go trials were delivered between each go trial. Trials were suspended when animals broke contact with the spout for >50 ms. To determine whether the animal detected the target, spout contact was monitored during the last 100 ms of each trial (cross-hatched region) and scored as a “yes” response if they were off the spout for at least 50 ms. A 300 ms aversive stimulus followed each go trial (black). Middle and bottom images are shown on the same timescale; the temporal relationship of the fine structure examples in the top image are indicated by the gray background.

cue. Go (i.e., FM) and no go (i.e., no modulation) trials were scored by determining whether the animal broke contact with the spout for at least 50 ms during the last 100 ms of the trial period (Fig. 1). Breaking contact with the spout for ≥ 50 ms was scored as a hit on go trials and as a false alarm on no go trials.

The first few sessions consisted of procedural training during which a series of go trials consisting of 500 Hz FM depth were presented by the experimenter until the gerbils responded correctly on at least 7 out of 10 consecutive go trials. Once this criterion was reached, we tested animals on a range of at least 5 FM depths within each session, presented in descending order from largest to smallest. An animal's performance on the previous session determined the range of depths on which it was tested during the following session (i.e., always bracketing the previous threshold). Three to five no go trials were delivered in between each go trial, randomized to avoid temporal conditioning. Because animals display between-subject variability in pain sensitivity (Mogil, 1999), we adjusted the shock level for each animal to reliably produce withdrawal from the spout, but not so great as to dissuade the animal from approaching the spout on subsequent trials. The shock was turned off for the two hardest FM depths being assessed in the series. Our logic was that animals performing a near-threshold detection task could easily fail to detect the conditioned stimulus. If so, the unconditioned stimulus would effectively train animals to avoid the water spout entirely or adopt a strategy that is associated with a high false alarm rate (e.g., pecking at the water spout).

However, this paradigm could have differentially conditioned the animals to respond only to the reinforced FM depths, but not unreinforced depths (Wagner and Rescorla, 1972; LoLordo and Fairless, 1985). Although there are many factors in our study that differ from standard differential conditioning paradigms (e.g., the use of smaller FM depths on successive days), we performed a control experiment to determine whether the lack of negative reinforcement for all depths led to artificially elevated FM thresholds. Five normal-hearing gerbils were run on the paradigm described above, except the shock was delivered for all FM depths. These animals displayed an average FM depth threshold of 94 (SD 33) Hz ($\log_{10}\text{Hz} = 1.95$, SD 0.13). This performance was significantly poorer than that observed in normal hearing controls that did not have reinforcement at the hardest FM depths.

Tone thresholds were determined using the same behavioral procedure described for FM threshold assessment. A 1 s tone (2.5 ms cos² onset/offset envelope) was used for the go trials with silence during the no go and intertrial periods. Tone level was varied in 5 dB steps and the animal's threshold performance on the previous session determined the range of levels on which it was tested during the next session (i.e., always bracketing the previous threshold). Because we only tested tone thresholds for three to five sessions, the session with the best threshold was selected as the animal's threshold. Two of the control adults tested did not perform a sufficient number of trials to assess their tone thresholds and were removed from the analysis of sensation level.

Experiment setup. Gerbils were placed in a small cage within an acoustic isolation booth and observed in a separate room via a closed circuit monitor. The test cage contained a stainless steel drinking spout and metal floor plate that formed the terminals of a circuit through which a mild aversive shock could be delivered at the end of warning trials (Sarro and Sanes, 2010). Spout contact was monitored via a custom-built circuit that used a 940 nm infrared LED (LTE 302; Lite-On) and photodiode (OP950; Optek Technology) contained in custom housing (Techwell Solutions). This circuit could also be used to deliver a mild aversive shock at the end of warning trials. Stimuli were digitally generated using a real-time processor (RZ6; Tucker-Davis Technologies) and delivered via a single free-field speaker (DX25TG05-04; Vifa) positioned 1 m in front of the lick spout. The speaker was calibrated using a spectrum analyzer (Brüel and Kjær) via a 1/4 inch free-field condenser microphone (Brüel and Kjær) positioned 1 cm above the spout.

Data analysis. Percent yes (i.e., similar to percent correct except the no go value is included) functions from sessions consisting of at least five presentations of five different depths were fitted using the open-source package psignifit. This package can fit several different psychometric functions and allows the specification of prior probability distributions for each parameter (e.g., guessing and lapsing rate). For this study, a psychometric function representing a linear transform of stimulus intensity values (i.e., the "mw0.1" core available in the bootstrap inference algorithm) fitted by a right gumbel sigmoid produced a reasonable fit to most of our data. The function is described as follows:

$$\Psi(x; m, w, \gamma, \lambda) = \gamma + (1 - \gamma - \lambda)$$

$$F(x; m, w)$$

where:

$$F(x; m, w) = \exp\left(-\exp\left(-\frac{z(\delta) - z(1 - \delta)}{w}(x - m) - z(0.5)\right)\right)$$

and:

$$z(\delta) = \log(-\log(\delta)).$$

Here, x represents stimulus difficulty, m the midpoint, w the width of the interval over which $F(x; m, w)$ rises from δ to $1 - \delta$ (in psignifit's documentation, δ is referred to as α ; however, we use δ to differentiate it from the α parameter of the beta prior described below), λ is the lapse rate, and γ is the FA rate. Both m and w were unconstrained and δ was fixed at 0.1 (the default value set by psignifit). The prior distribution for the FA rate, γ , was specified as a beta distribution with the mode fixed at

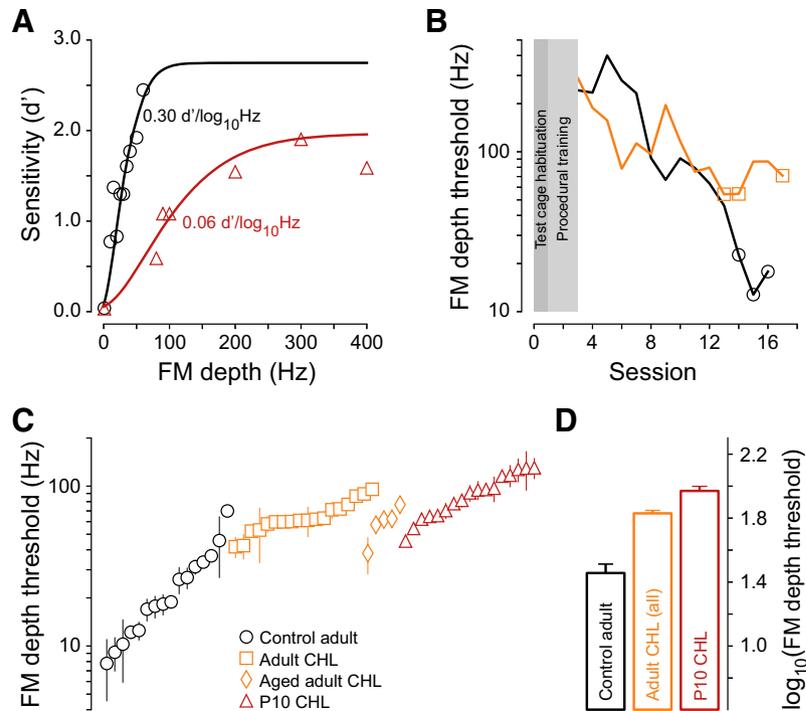


Figure 2. FM depth detection thresholds were worse in animals with CHL. **A**, Example psychometric functions from a single test session for a control (black) and P10 CHL (red) animal. FM depth threshold was estimated by fitting a psychometric function (solid line) to the percent-correct data (individual points). The fitted psychometric function was transformed into sensitivity (d') using the fitted FA rate. Threshold was defined as the FM depth where $d' = 1$. The slope is indicated next to both curves. **B**, FM depth threshold for each session for a representative control (black) and adult CHL animal (orange). The first session was devoted to test cage habituation (dark gray), followed by several sessions of procedural learning (i.e., training at a single FM depth of 500 Hz, light gray). Filled markers indicate the three best sessions. **C**, Average of the three best FM depth thresholds for each animal. Bars indicate \pm SEM. The aged adult CHL group is plotted separately (diamond marker). In all other panels and figures, the aged adult CHL group was combined with the adult CHL group. **D**, Average FM depth threshold for each group. Bars indicate \pm SEM.

the empirical FA rate for that session by setting the distribution parameters, α and β , to $N_{FA} + 1$ and $N_{CR} + 1$. Following guidelines described in Fründ, Haenel and Wichmann (2011), the prior for the lapsing rate, λ , was set to a mode of 0.05 (i.e., $\alpha = 1.5, \beta = 12$). These prior distributions allowed us to specify the most likely value for the guess rate based on our empirical observations.

As illustrated in Figure 2A, fitted functions were transformed to a d' metric, defined as $Z(\text{hit fraction}) - Z(\text{FA fraction})$, which normalizes performance relative to the FA rate for a given session. Threshold was defined as the FM depth at which performance reached a d' of 1. To ensure that fits were of sufficient quality, we discarded fits in which the deviance of the fit to the original dataset exceeded the 95th percentile of the deviance of the fit to 1000 simulated datasets (for details, see Fründ et al., 2011).

Because animal behavior can be variable from session to session due to various factors (e.g., motivation, attention, confidence in the task), we considered several approaches to estimating the psychometric threshold of each animal. One straightforward approach is to calculate the asymptotic threshold (e.g., the average of the last three sessions) regardless of how well the animal was performing over these sessions. However, this approach could give greater weight to poor performance that reflected behavioral, rather than sensory, factors. An alternate approach is to select the three sessions with the best FM depth thresholds after a specific training period (markers in Fig. 2B). The average of the three best thresholds were generally better than the average threshold over the final 3 d of testing (data not shown), suggesting that some animals lost motivation in the task toward the end of the experiment. Regardless of the approach for selecting the three sessions to average, a single-factor ANOVA test reports similar levels of significance when comparing the treatment groups on the various parameters tested (e.g., FM depth threshold, FA rate, lapse rate, psychometric slope, etc.). Because the choice of assessing psycho-

metric threshold did not affect the final outcome—that is, the statistical significance of between-group differences—subsequent analysis focuses on the three best sessions from each animal.

Statistical tests were first performed to determine whether the dependent variable was normally distributed for each treatment group (control, adult CHL, P10 CHL), using a Shapiro–Wilk normality test. Although there were only five departures from normality out of 21 combinations (slope of psychometric function and FA rate for adult CHL animals, $p < 0.0001$ and $p = 0.0006$, respectively; sensation level for P10 CHL, $p = 0.02$; slope of psychometric function and lapsing rate for control adults, $p = 0.02$ and $p = 0.03$, respectively), we used Levene's test for equal variance (using the median value as an estimate of each group's center) because it is more robust when samples deviate from a normal distribution. Of all of the dependent variables tested, only 2 had unequal variance (FM thresholds, $df = 2$, F -value = 8.99, $p = 0.0004$; slope of psychometric function, $df = 2$, F -value = 7.74, $p = 0.001$). For all multiple-comparison tests, we used the nonparametric Kruskal–Wallis test followed by pairwise comparisons using a two-sided Wilcoxon test with Holm-corrected p -values.

The statistical significance of the correlation, ρ , between variables was assessed by randomly shuffling the original dataset and computing the correlation statistic on this shuffled set. This process was repeated at least 10,000 times to generate a reference distribution, ρ^* , and the two-sided p -value was computed as the fraction of the distribution that exceeded the actual statistic as follows:

$$\frac{\sum_{n=1000} |\rho^*| \geq |\rho|}{n}$$

Results

CHL impairs detection of frequency modulation

To evaluate the FM detection thresholds as a function of hearing status, psychometric functions were obtained from three groups of adult gerbils (see Materials and Methods): adults with normal-hearing ($n = 16$), adults raised with CHL induced at P10 ($n = 17$), and adults with CHL induced at P83 ($n = 23$). On average, normal-hearing adult gerbils displayed FM depth thresholds of 25 (SD 16) Hz ($\log_{10}\text{Hz} = 1.31$, SD 0.27). This value suggests that FM detection is superior to chinchillas (≈ 100 Hz; Long and Clark, 1984) and close to normal-hearing humans (≈ 10 Hz; Shower and Biddulph, 1931; ≈ 20 Hz; Sek, 1994).

In contrast to controls, both adult CHL and P10 CHL animals displayed poorer detection thresholds of 64 (SD 15) Hz ($\log_{10}\text{Hz} = 1.80$, SD 0.10) and 89 (SD 27) Hz ($\log_{10}\text{Hz} = 1.93$, SD 0.14), respectively. There was a large range of FM thresholds with a degree of overlap between groups (Fig. 2C). The best adult CHL animals displayed performance on par with that of the worst normal-hearing controls. Likewise, the best half of the P10 CHL animals had performance comparable to the worst half of the adult CHL group. To test for significance, FM depth thresholds were converted to \log_{10} values because this is the likely decision variable for frequency discrimination (Demany and Semal, 1989; Moore and Sek, 1996). A Kruskal–Wallis test reported a main effect of group ($\chi^2 = 34.5$, $df = 2$, $p < 0.0001$). A Wilcoxon test using Holm-corrected p -values demonstrated significant differences between each group pair (control vs adult CHL: $df = 1$, $p < 0.0001$; control vs P10 CHL: $df = 1$, $p < 0.0001$; P10 CHL vs adult CHL: $df = 1$, $p = 0.0008$). Therefore, CHL impairs performance regardless of age of onset, but the impairment is greater when hearing loss is induced during early development (Fig. 2D).

To determine whether CHL resulted in a general decrease in sensitivity to differences in stimulus magnitude, the slope of the psychometric function at $d' = 1$ was measured for the three best sessions. As shown in Figure 3, the average psychometric function slope was shallower in animals with CHL whether induced at

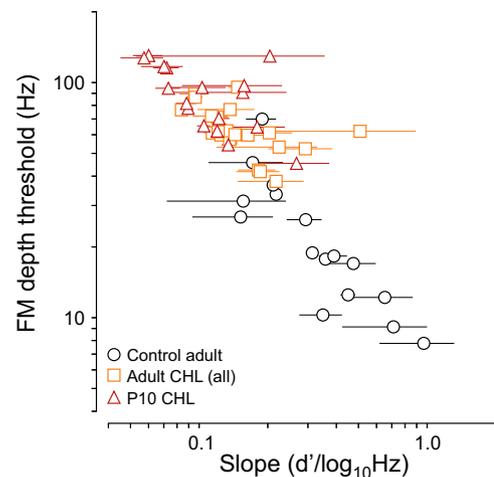


Figure 3. Psychometric function slopes were shallower and performance was more variable for animals with CHL. Each animal's FM psychometric function slope, $d'/\log_{10}(\text{Hz})$, is plotted against the FM detection threshold. The psychometric function slopes were steepest for control animals. Furthermore, there was a significant correlation between threshold and slope for all animals. Values were obtained from the psychometric functions with the three best FM depth threshold values, as described in Figure 2B. Error bars indicate \pm SEM.

P10 or in adulthood. A Kruskal–Wallis test reported a main effect of group ($\chi^2 = 25.6$, $df = 2$, $p < 0.0001$). A Wilcoxon test using Holm-corrected p -values was performed on group pairs and demonstrated significant differences between each (control vs adult CHL: $df = 1$, $p < 0.0001$; control vs P10 CHL: $df = 1$, $p < 0.0001$; P10 CHL vs adult CHL: $df = 1$, $p = 0.03$). In addition, there was a strong negative correlation between FM detection threshold and slope (Spearman's rank correlation, $\rho = -0.79$; permutation test, $p < 0.0001$). This result suggests that normal hearing animals could discriminate smaller stimulus differences (i.e., steep slope) compared with CHL animals (i.e., very shallow slope).

Poorer FM detection is not explained by sensation level or task performance

Human psychophysical data suggest that FM detection improves with increasing sensation level (i.e., loudness of the signal relative to the subject's threshold). To investigate whether this could explain the impaired performance in CHL animals, we assessed 4 kHz tone behavioral thresholds after completion of the FM detection testing in all but six normal-hearing adults to determine the sensation level at which each animal performed the FM detection task. The absolute thresholds for the three groups were 28.2 (SD 12.2) dB SPL for controls, 59.4 (SD 11.2) dB SPL for P10 CHL animals, and 56.3 (SD 10.2) dB SPL for adult CHL animals. This demonstrates that the CHL procedure introduces a 30 dB hearing loss regardless of age of onset and translates to an average sensation level of 19.9 (SD 7.1) dB for control adults, 33.4 (SD 12.7) dB for P10 CHL, and 36.4 (SD 11.6) dB for adult CHL animals (Fig. 4A). A Kruskal–Wallis test reported a significant effect of group ($\chi^2 = 12.0$, $df = 2$, $p = 0.002$). However, a *post hoc* Wilcoxon test using Holm-corrected p -values revealed no significant difference between P10 and adult CHL animals ($p = 0.48$), indicating that CHL induced a similar level of attenuation in both groups. In contrast, the control adults were run at a lower sensation level relative to both the P10 ($p = 0.03$) and adult CHL ($p = 0.001$) groups. This indicates that, if anything, the CHL animals had an advantage in terms of sound level and that sensation level was not a factor that could explain the impaired performance.

If CHL animals performed poorly on FM detection regardless of stimulus difficulty, then the elevated thresholds could reflect a general cognitive problem in performing the behavioral task. To investigate whether the within-group variance and cross-group differences could be explained by poor task performance, we examined four performance metrics: false alarm rate, lapsing rate (i.e., miss on easy trials), sensitivity at the easiest FM depth, and reaction time. The results of these analyses suggest that there were no systematic between-group differences in performance that could explain the differences in FM detection thresholds.

FA rate (the probability of an incorrect response when the signal is not presented) is influenced in part by the animal's decision process (i.e., the criterion or threshold above which they will produce a "yes" response). This decision process, in turn, is influenced by various factors, including the shock level and task difficulty. Therefore, systematic differences in FA rate between groups may suggest that we failed to treat these groups equally in adjusting the aversive stimulus or selecting the appropriate sequence of values to test them on each day. With the exception of one animal, the majority of CHL animals had FA rates comparable to those of the control adult group (Fig. 4B). In fact, the animals with the highest and lowest FM thresholds had the lowest FA rates (data not shown) and there was no correlation between FM threshold and FA rate (permutation test using Spearman's rank-order, $p = 0.71$). A Kruskal–Wallis test reported no effect of group ($\chi^2 = 1.8$, $df = 2$, $p = 0.41$). Therefore, it is unlikely that dissimilarities in the testing procedure could explain the group differences in FM detection threshold.

Lapsing rate (the probability of an incorrect response independent of stimulus intensity) has been used as a proxy for attention. This rate reflects the upper asymptote of the psychometric function, placing an upper bound (1-lapsing rate) on the maximum fraction correct the animal can be expected to achieve regardless of stimulus intensity. Inattentive animals would tend to miss particularly easy FM depths, resulting in a higher lapsing rate. Here, performance on the easiest FM depth in each session was used as a means of estimating lapsing rate. There was no systematic relationship between lapsing rate and FM thresholds (permutation test using Spearman's rank-order, $p = 0.21$), nor was there a significant difference between groups (Fig. 4C; Kruskal–Wallis, $\chi^2 = 4.8$, $df = 2$, $p = 0.09$). *Post hoc* pairwise comparisons revealed no significant differences between groups. A related measure of performance is sensitivity (d') at asymptotic performance. Although there was no systematic relationship between d' at the easiest stimulus depth and FM thresholds (permutation test using Spearman's rank-order, $p = 0.69$), there was a modest difference between group (Kruskal–Wallis, $\chi^2 = 5.9$, $df = 2$, $p = 0.05$), with CHL groups displaying slightly better asymptotic sensitivity (Fig. 4D). *Post hoc* pairwise comparisons revealed no significant differences between groups. We also investigated the estimate of lapsing rate and d' at asymptotic performance using our fitted data and found no significant between-group differences (Kruskal–

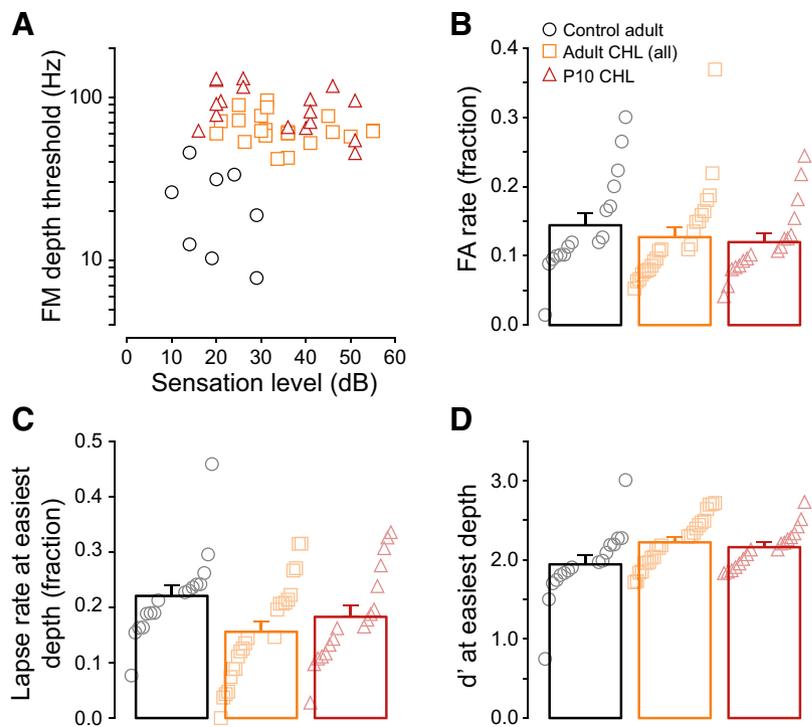


Figure 4. The FM depth detection thresholds were not correlated with sensation level (A) and there was no between-group difference for FA rate (B), lapse rate on the easiest FM depth (C), or sensitivity at the easiest stimulus depth (D). Data presented in all plots are averaged from the animal's three best sessions, as described in Figure 2B. Error bars indicate SEM.

Wallis) or systematic relationship between lapsing rate and FM thresholds (permutation test using Spearman's rank-order).

Reaction time has been associated with task difficulty, sustained attention or vigilance, and the speed-accuracy trade-off (Cattell, 1886; Saltzman and Garner, 1948; Buck, 1966; Luce and Green, 1972; Teichner and Krebs, 1972; Weissberg et al., 1990; Salthouse and Hedden, 2002). Although the meaning of reaction time with respect to the behavioral procedure is subject to interpretation, it was used as a quantitative measure of performance to further establish the lack of behavioral differences between the groups. The probability of spout contact was calculated as a function of trial duration for all "hit" responses near each animal's FM detection threshold. Because animals typically do not return to the spout until after the trial is over, this measure can be interpreted as the cumulative distribution function of reaction time (e.g., the cumulative probability that the animal will have responded by a certain point in time). Steeper slopes indicate that the animal has a tendency to respond around a certain point in time, whereas slopes closer to unity indicate that reaction times are uniformly distributed throughout the trial. As shown in Figure 5A, there were no group differences in the probability of spout contact during threshold go trials. Similarly, there were no group differences for miss trials (Fig. 5A). For all groups, the probability of being off the spout on threshold go trials increased by 0.1 for every 100 ms increment of stimulus after the first 300 ms.

To obtain a single reaction time value for each animal, we measured the average time at which the animal first leaves the spout on go trials that were scored as a "hit," even if the animal returned briefly to the spout later in the trial (this eventuality is illustrated in Fig. 5A for the hit trials; there is a marginal increase in probability of being on the spout after 950 ms). As shown in Figure 5B, the mean reaction time for suprathreshold values is ≈ 515 ms across all treatment groups with no significant group

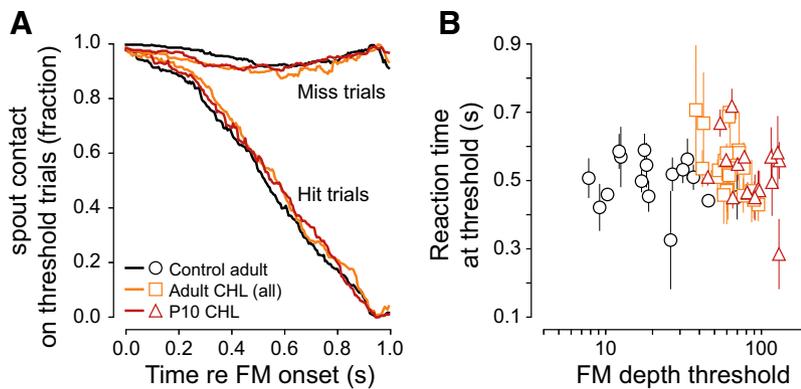


Figure 5. Reaction time was nearly identical across control and CHL groups. **A**, Average probability of spout contact relative to onset of frequency modulation is shown for hit trials near the animals' threshold. For reference, spout contact on miss trials are plotted as well. Although we required the animal to be on the spout before presenting a trial, there is a non-negligible chance of the animal leaving the spout just before the trial begins. Even though the animal may have been off the spout by the end of some miss trials, it was not scored as a hit because it did not meet the criterion of being off the spout for at least 50 ms. **B**, Reaction time for individual trials was computed as the time at which the animal first left the spout regardless of whether they chose to return to the spout. Reaction time at threshold was not correlated with the animal's FM depth threshold and there were no between-group differences. Error bars indicate \pm SEM.

differences (Kruskal–Wallis, $\chi^2 = 1.76$, $df = 2$, $p = 0.41$) and is not correlated with FM threshold (permutation test using Spearman's rank-order, $p = 0.44$). The consistent between-group performance on these four metrics indicates that the animals in each treatment group performed the FM detection task in a nearly identical manner.

Discussion

The neural consequences of altered sensory experience are most profound during development, often referred to as sensitive periods. For example, when cochlear prostheses are implanted in deaf subjects during the first 18 postnatal months, they achieve better cortical activation compared with subjects implanted at a later age (Ponton and Eggermont, 2001; Sharma et al., 2002; Kral and Sharma, 2012). These neurophysiological outcomes are consistent with behavioral data that demonstrate better speech production and language acquisition in subjects who receive implants at a younger age (Svirsky et al., 2004; Niparko et al., 2010). Similarly, clinical studies on visual deprivation (e.g., cataracts) suggest the existence of multiple sensitive periods (Lewis and Maurer, 2005; Scheiman et al., 2005).

Despite firm evidence for sensitive periods, hearing loss-induced changes to central auditory function are also well documented in adulthood, especially during senescence (Syka, 2002, 2010; Chisolm et al., 2003; Caspary et al., 2008; Turner et al., 2013). Regardless of age of onset, both short- and long-term auditory deprivation are associated with measurable changes in sensory and cognitive function (Moore et al., 1996; Formby et al., 2003; Munro and Blount, 2009; Lin et al., 2011; Seldran et al., 2011; Humes et al., 2012). Similarly, environmental manipulations that provide supplemental sound exposure suggest that some forms of plasticity are present in adulthood (Pienkowski and Eggermont, 2011). Therefore, this study was designed to determine whether an auditory percept, FM detection, was affected by the same CHL manipulation induced either before neural and behavioral properties are mature (P10, ear canal opening) or after they reach an adult state (P83). The results demonstrate that CHL induced at either age leads to poorer FM detection. However, the effect was larger when CHL was induced during early development.

Age-dependent effect of hearing loss onset

If the neural properties that are impaired by hearing loss during a sensitive period are causally related to auditory perception, then juvenile onset hearing loss would have a greater impact on perception than the same manipulation commencing in adulthood. To test this idea, we induced CHL via bilateral malleus removal. This form of CHL raises air conduction thresholds, but not bone conduction thresholds, indicating that there is no damage to the cochlea (Tucci et al., 1999). This minimized the potential contribution of cochlear processing deficits (Oxenham and Bacon, 2003). In fact, children with chronic otitis media often experience transient hearing loss without damage to the cochlea and this deprivation is thought to impair neural and perceptual development (Whitton and Polley, 2011). Furthermore, unilateral CHL during development can impair bin-

aural processing and speech detection in noise (Clements and Kelly, 1978; Knudsen et al., 1984a, 1984b; Moore et al., 1999; Parsons et al., 1999; King et al., 2000). Longer durations of unilateral CHL, due to the congenital absence of an ear canal, are associated with a poorer ability to understand speech in the presence of noise after corrective surgery, suggesting termination of the sensitive period for recovery (Gray et al., 2009).

Given an equivalent elevation of hearing thresholds, the animals that experienced CHL from the age of ear canal opening displayed poorer FM detection relative to animals that experienced CHL beginning in adulthood (Figs. 2, 3). Because measures of audibility and proxies for nonsensory factors showed no difference between the CHL groups, these results indicate that the developing nervous system is more vulnerable to the manipulation. However, the noteworthy finding is that adult onset hearing loss led to a significant impairment of FM detection. This result is consistent with a human study in which a similar carrier and modulation frequency were tested, yielding FM detection thresholds < 16 Hz for control subjects and ≈ 90 Hz for elderly subjects with moderate hearing loss (Moore and Skrodzka, 2002). These results imply that the neural properties used to define a sensitive period are not exclusive correlates for a specific perceptual deficit.

Alternative explanations for the effect of CHL

One explanation for the results could be that the signals were not sufficiently audible to animals with CHL. However, 4 kHz behavioral thresholds did not differ between CHL groups and stimuli were usually delivered at a higher sensation level for CHL animal (Fig. 4A). It is also possible that nonsensory factors such as attention contributed to the poorer FM detection thresholds displayed by CHL animals. Asymptotic performance is used as an indirect measure of attention in children (Bargones et al., 1995), false alarm rate has been used as a proxy for sustained attention (Lin et al., 1999; Kanaka et al., 2008), and reaction time is associated with accuracy and task difficulty (Cattell, 1886; Saltzman and Garner, 1948; Buck, 1966; Luce and Green, 1972; Teichner and Krebs, 1972; Weissberg et al., 1990; Salthouse and Hedden, 2002). To the extent that these measures assess nonsensory factors, there was

no indication of a difference between the control and CHL groups (Figs. 4, 5).

The duration of hearing loss is a key variable often correlated with the age of onset and may confound interpretation of the effect of age of onset. For prelingually deafened humans who receive a cochlear prosthesis, a longer duration of auditory deprivation is associated with poorer auditory perceptual skills, including speech comprehension (Tong et al., 1988; Busby et al., 1992, 1993; Schramm et al., 2002; Svirsky et al., 2004; McConkey Robbins et al., 2004; Niparko et al., 2010). A similar outcome has been reported for postlingually deafened cochlear implant listeners (Gantz et al., 1993; Blamey et al., 1996; Rubinstein et al., 1999). In apparent contrast, hearing loss at an earlier age and/or for a longer duration is associated with better speech recognition for a group of 20 subjects with severely elevated high-frequency thresholds (Seldran et al., 2011). Because most human subjects receive remediation of some sort (e.g., auditory prostheses, speech therapy), it is difficult to determine the influence of learning or acclimatization-driven neural plasticity mechanisms (Turner et al., 1996). Here, we demonstrate that juvenile-onset CHL impairs FM detection, even when compared with adult-onset CHL animals that are matched for duration of sensory deprivation.

Finally, it is possible that animals attended to small amplitude modulation (AM) in the stimulus. Using the speaker calibration, we calculated the maximum level change that would be expected for the average FM depth detection threshold values of each group, and compared this with published AM detection thresholds. For controls (25 Hz), the stimulus contained a 1.4 dB level change. This is smaller than the adult AM detection threshold (3.4 dB) calculated from Rosen et al. (2012), suggesting that controls did not use an AM cue. For P10 CHLs (89 Hz), the stimulus contained a 6.2 dB level change. This is larger than the P10 CHL AM detection threshold (4.5 dB) calculated from Rosen et al. (2012), suggesting that P10 CHLs could have used an AM cue. If CHL animals did exploit the intensity cues to assist in detecting the FM tone, then they may have even poorer FM depth thresholds than reported here. However, P10 CHL animals had access to the same acoustic information as the adult CHL animals, yet displayed a deficit in perception relative to adult CHL that cannot be attributed to non-sensory factors. When compared to normal-hearing adults, it remains possible that both CHL groups used sound level information to augment their FM detection performance.

Relationship to neural consequences of conductive hearing loss

By several measures, the effect of CHL on the CNS depends on age of onset. Bilateral CHL has a smaller affect on 2-deoxyglucose uptake, a measure of metabolic activity, when it is induced in adult compared with P21 or younger gerbils (Tucci et al., 1999). Similarly, unilateral CHL has a smaller affect on neural activity, as assessed by Mn²⁺-enhanced magnetic resonance imaging, when induced at P21 compared with P10 mice (Yu et al., 2005). However, unilateral CHL can produce both age-dependent and age-independent effects in auditory cortex. Tonotopy is affected when CHL begins before P28, responses from the unmanipulated ear are augmented when CHL begins at P28, and responses from the manipulated ear are suppressed even when CHL begins in adulthood (Popescu and Polley, 2010). Furthermore, depending on the auditory processing metric under study, the effects due to hearing loss can display quite specific critical periods (Polley et al., 2013). It has been suggested that heightened sensitivity of the developing system to hearing loss is due to an extended period

during which synapse formation and elimination is occurring in auditory cortex (Kral and Sharma, 2012). These neural findings are consistent with our result of poorer FM detection thresholds in both age groups, with a greater effect for animals with juvenile-onset CHL (Fig. 2).

The large perceptual effect of adult CHL cannot be explained entirely by the cellular changes that occur following early onset CHL (Xu et al., 2007, 2010; Takesian et al., 2010). For example, CHL leads to a reduction in the strength of cortical inhibition when induced at P10, but not at P83 (Takesian et al., 2012). In contrast, the weaker inhibition that accompanies adult onset hearing loss may involve changes to GABA content and release (Bledsoe et al., 1995; Ling et al., 2005; Caspary et al., 2008). Therefore, our findings can serve to distinguish neural properties that display an early sensitive period and are more likely to differentiate the effects of juvenile hearing loss from those that are not sensitive to age of deprivation, and may explain the perceptual effect of adult-onset CHL.

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