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Research paper

# Rapid measurement of auditory filter shape in mice using the auditory brainstem response and notched noise

Ioan A. Lina, Amanda M. Lauer*

*Johns Hopkins University School of Medicine, Department of Otolaryngology – HNS, Center for Hearing and Balance, 515 Traylor, 720 Rutland Ave., Baltimore, MD 21205, United States*

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ABSTRACT

The notched noise method is an effective procedure for measuring frequency resolution and auditory filter shapes in both human and animal models of hearing. Briefly, auditory filter shape and bandwidth estimates are derived from masked thresholds for tones presented in noise containing widening spectral notches. As the spectral notch widens, increasingly less of the noise falls within the auditory filter and the tone becomes more detectible until the notch width exceeds the filter bandwidth. Behavioral procedures have been used for the derivation of notched noise auditory filter shapes in mice; however, the time and effort needed to train and test animals on these tasks renders a constraint on the widespread application of this testing method. As an alternative procedure, we combined relatively non-invasive auditory brainstem response (ABR) measurements and the notched noise method to estimate auditory filters in normal-hearing mice at center frequencies of 8, 11.2, and 16 kHz. A complete set of simultaneous masked thresholds for a particular tone frequency were obtained in about an hour. ABR-derived filter bandwidths broadened with increasing frequency, consistent with previous studies. The ABR notched noise procedure provides a fast alternative to estimating frequency selectivity in mice that is well-suited to high through-put or time-sensitive screening.

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## 1. Introduction

Mouse models have gained increasing importance for understanding the genetic and environmental contributions to the development of hearing function as well as the mechanisms underlying deafness and other hearing disorders. Basic hearing sensitivity is now routinely screened in mouse models of auditory function. However, common hearing screening protocols used in mice are often insensitive to detecting auditory dysfunction beyond elevated thresholds for sounds in quiet or reduced reactivity to loud sounds. Important information regarding auditory function may be missed when relying on these measures since animals can display significant deficits while maintaining normal pure tone thresholds (e.g., Kujawa and Liberman, 2009; Lauer and May, 2011; Allen and Ison, 2012; Satheesh et al., 2012).

Frequency resolution affects the ability to separate out components of complex sounds, detect sounds in background noise, and distinguish two sounds that are close together in frequency. Damage to the auditory system alters frequency resolution (e.g., Patterson et al., 1982; Tyler et al., 1984), contributing to common complaints of difficulty resolving sounds in the presence of competing backgrounds. Traditional behavioral measures of frequency selectivity are inefficient when considering animal models of developmental processes, early-onset hearing deficits, or models with rapidly declining hearing due to lengthy training and testing times. Our goal is to develop efficient, behaviorally validated methods to screen complex auditory functions in mice using rapidly measured evoked potentials. To that end, we describe a procedure using auditory brainstem responses (ABRs) measured in simultaneous spectrally notched noise to estimate peripheral frequency selectivity in mice.

The notched noise procedure characterizes frequency resolution based on the presentation of a pure tone in background noise containing a spectral notch (Fig. 1). According to the power spectrum model of masking, increasing the width of the notch results in less noise interference within an auditory filter until a "critical band" is reached where further increases in notch width no longer cause a change in threshold (Patterson, 1974). These theoretical auditory filters can be approximated using a rounded exponential (roex) minimization algorithm in order to estimate the critical bandwidth as an equivalent rectangular bandwidth (ERB) value

*List of abbreviations:* ABR, auditory brainstem response; dB, decibel; Hz, Hertz; ERB, equivalent rectangular bandwidth.

* Corresponding author. Tel.: +1 443 287 6336; fax: +1 410 955 1299.
*E-mail address:* alauer2@jhmi.edu (A.M. Lauer).

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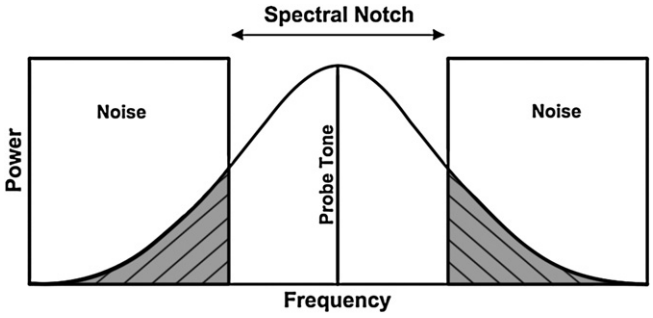


**Fig. 1.** Schematic of the notched noise method of estimating auditory filter bandwidth. Thresholds are measured for a probe tone presented in the presence of broadband noise containing a spectral notch centered on the probe tone frequency. The shaded portions of the figure represent the noise energy falling inside the filter that masks the probe tone frequency. As the notch is widened, less and less energy falls within the auditory filter rendering the tone more detectible.

(Glasberg and Moore, 1990). In the present paper, we evaluate the effectiveness of using the ABR and notched noise procedure as a rapid method for assessing auditory filter bandwidth in mice.

The notched noise procedure is based on well-established psychoacoustic behavioral methods that have only been implemented in a small sample of animals (Marean et al., 1993; Niemiec and Shoffner, 1990; Lin et al., 1997; Finneran et al., 2002; Lemmonds et al., 2012; May et al., 2006). Similar stimuli have been used in conjunction with ABRs to rapidly estimate auditory frequency selectivity in wild birds and dolphins (Popov et al., 1997; Gall and Lucas, 2010; Henry and Lucas, 2010a, b). This paradigm yields a reasonable estimate of auditory filters at a range of frequencies within several hours rather than the months to a year required for behavioral procedures. The ABR procedure is ideal for models that may be difficult to test behaviorally, show rapid auditory system degeneration, or require testing of many animals. Moreover, these tests can be repeated at multiple time points over the course of development, aging, or treatment.

## 2. Material and methods

### 2.1. Subjects

A total of 17 CBA/CaJ mice were bred and housed in a quiet vivarium to minimize exposure to potentially damaging environmental noise (Lauer et al., 2009). Ad libitum access to food and water was provided to all subjects. Ages of tested mice ranged from 6 to 28 weeks. Hearing status remains normal in this strain throughout this age range, and normal hearing was confirmed by measuring thresholds for clicks and tones presented in quiet for each test frequency. Seven mice were tested at each probe tone frequency with 4 mice tested at multiple frequencies. All procedures were approved by the Johns Hopkins University Animal Care and Use Committee, and were consistent with the Guide for the Care and Use of Laboratory Animals.

### 2.2. General auditory brainstem response procedures

Auditory brainstem response procedures were based on previously published work described by members of our research group (e.g. Ngan and May, 2001; May et al., 2002; Stamataki et al., 2006; Lauer and May, 2011; Yang et al., 2011). Mice were anesthetized with a solution of ketamine (100 mg/kg) and xylazine (20 mg/kg) in 14% ethyl alcohol such that 0.1 cc/per 20 g body weight were administered intraperitoneally. Anesthetized mice were placed on a gauze-covered heating pad and maintained at 37 °C ± 1° inside a sound-attenuating chamber lined with acoustic foam. ABRs were differentially recorded from the scalp using subcutaneous platinum needle electrodes placed over the left bulla and at the vertex of the skull. A ground electrode was inserted into the ipsilateral hind leg muscle. Heart rate, breathing, and relative movement were monitored throughout the experiment using an audio monitor and an oscilloscope. If an animal showed signs of waking at any time during recording, supplemental doses of 1/3 to 1/2 the original anesthesia dose were administered. Stimulus generation and collection of ABR responses were controlled using custom Matlab-based software interfaced with Tucker Davis Technologies (TDT) hardware. Stimuli were amplified using a Crown amplifier and played through a Fostex dome tweeter speaker (model FT28D) or a pair of Radioshack Supertweeters located 30 cm from the vertex of the skull and aligned with the median sagittal plane of the animal. A stimulus presentation rate of 10/s was used throughout the experiment. Responses were amplified using a World Precision Instruments ISO-80 biological amplifier and filtered between 30 and 3000 Hz using a Krohn-Hite bandpass filter. Speaker calibration was performed using a 1/4-in Brüel and Kjær free field microphone, TDT hardware, and custom Matlab-based software. Periodic calibration checks were performed using a Larson-Davis LXT sound level meter fitted with a 1/2-in free field microphone throughout the experiment.

Responses were recorded for a period of 30 ms beginning with stimulus onset; ABR waves occurred within approximately 2–10 ms of stimulus onset (Fig. 2A). Thus, 0 ms indicates the time of stimulus onset in Fig. 2A. Since the presence of continuous background noise maskers often degraded the ABR signal such that it was difficult to clearly discern each wave as distinct from wavelets or merged waves at low probe tone levels, the magnitude of the ABR was determined by calculating the maximum peak-to-peak amplitude (any wave) within an 8 ms window beginning 2 ms after stimulus onset. ABR waveforms recorded in the presence of noise with spectral information near the probe frequency (small notch width) are often de-synchronized and of poor quality compared to non-masked waveforms (e.g., Van Zanten and Brocaar, 1984; Nousak and Stapells, 2005). Typically, the largest peak-to-peak magnitude occurred between the first negative and the second positive waves. Baseline response noise magnitudes were calculated by averaging the last 10 ms of each averaged 30 ms trace (no stimulus occurred during this time). If a large deflection occurred during the baseline window, the recording was discarded and repeated. This was an extremely rare occurrence. The ABR and baseline time windows are depicted in Fig. 2A.

Stimuli were first presented well above threshold to confirm the presence of a robust response and then attenuated in 10 or 20 dB steps to obtain a level series. Step size was reduced to 5 dB near threshold. Stimulus level was decreased until a response was no longer visible. Threshold was defined as the interpolated sound level at which the ABR magnitude was 2 standard deviations (SD) above the average baseline noise level calculated from the individual baseline noise levels computed for each stimulus level tested (Fig. 2B). This procedure for determining threshold is in keeping with common procedures in mice and other nonhuman species in which ABR waveforms are easily differentiated from background noise (Ngan and May, 2001; May et al., 2002; Stamataki et al., 2006; Lauer and May, 2011; Yang et al., 2011; Walter et al., 2012). This objective criterion produced threshold estimates that were within a few dB of those obtained using a subjective visual inspection method but removed potential effects of observer bias. ABRs were averaged over 300 stimulus presentations for each condition. Pilot experiments in our lab have shown that increasing the number of repetitions does not improve the response waveform or the signal to noise ratio since the mouse ABR is a very robust response at

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