



Research Paper

The effects of aging and sex on detection of ultrasonic vocalizations by adult CBA/CaJ mice (*Mus musculus*)

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ABSTRACT

Mice are frequently used as animal models for human hearing research, yet their auditory capabilities have not been fully explored. Previous studies have established auditory threshold sensitivities for pure tone stimuli in CBA/CaJ mice using ABR and behavioral methodologies. Little is known about how they perceive their own ultrasonic vocalizations (USVs), and nothing is known about how aging influences this perception. The aim of the present study was to establish auditory threshold sensitivity for several USV types, as well as to track these thresholds across the mouse's lifespan. In order to determine how well mice detect these complex communication stimuli, several CBA/CaJ mice were trained and tested at various ages on a detection task using operant conditioning procedures. Results showed that mice were able to detect USVs into old age. Not surprisingly, thresholds differed for the different USV types. Male mice suffered greater hearing loss than females for all calls but not for 42 kHz tones. In conclusion, the results highlight the importance of studying complex signals across the lifespan.

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1. Introduction

Age-related hearing loss (ARHL), or presbycusis, is a universal feature of mammalian aging (Yamasoba et al., 2013). This condition is characterized by the progressive decrease in hearing sensitivity from high to low frequencies, as well as a decrease in complex auditory signal comprehension, such as speech (Huang and Tang, 2010); it is the most common etiology among elderly humans. Further, the percentage of elderly people experiencing problems with speech comprehension increases progressively with age. Deterioration of speech perception in humans could be due to limited explicit processing in working memory (Rönnerberg et al., 2008), but van Rooij and Plomp (1990) have argued that the deterioration of speech perception during aging can be largely accounted for by progressive high-frequency hearing loss.

Mice (*Mus musculus*) are frequently used as an animal model for human hearing research, due to the mouse cochlea being anatomically similar to the human cochlea (Zheng et al., 1999). One common strain for auditory research is the CBA/CaJ mouse. Radziwon et al. (2009) discovered that the CBA/CaJ strain showed

peak sensitivity, as measured by operant conditioning for pure tones, in the 8–24 kHz range, with higher thresholds for tones outside of this range. This pattern resembles auditory brainstem response (ABR) thresholds for CBA/CaJ mice (Henry, 2004; Zheng et al., 2009). However, ABR recordings yield higher overall thresholds across all frequencies, limiting their comparisons to auditory acuity in awake, behaving mice (Radziwon et al., 2009).

Other studies have used the CBA/CaJ mouse strain to study the physiological basis of hearing loss. Ohlemiller et al. (2010) explored hearing abilities of the CBA/CaJ strain at different ages using compound action potential (CAP) recordings. The authors observed that pure tone thresholds remained stable in this strain well into their first year of life, until middle adulthood, at which point CAP thresholds increase rapidly at high frequencies. Endocochlear potential decline and loss of stria marginal cells could explain this age-related threshold increase (Ohlemiller et al., 2010). Similar patterns are thought to be the basis of hearing loss in humans as well as other animals (Ohlemiller et al., 2006; Pauler et al., 1988). In another study on the effects of aging on the auditory abilities of CBA/CaJ mice, Zheng et al. (1999) used ABR recordings to trace correlates of age related hearing loss. They found that this mouse strain exhibited stable thresholds for 8, 16, and 32 kHz tones up to 39 weeks of age; however, thresholds increased at all frequencies by 47 weeks of age.

In humans, there are known sex differences in ARHL, with males

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losing high frequency hearing earlier and becoming progressively less sensitive as they age (Corso, 1963; Gates and Cooper, 1991; Tambs et al., 2003). Longitudinal studies showed that hearing loss occurs twice as fast in men as it does in women in similar noise environments (Pearson et al., 1995). A similar pattern has also been observed in the CBA/CaJ strain of mouse. Henry (2004) examined hearing loss sex differences in the CBA/CaJ mouse model using ABRs, discovering that CBA/CaJ males exhibit poor high frequency thresholds earlier than females. Additionally, male mice had higher ABR thresholds for the high frequency hearing range up to middle adulthood. This pattern mimics human hearing loss and suggests that the CBA/CaJ mouse strain is an excellent animal model for studying ARHL.

As reviewed above, researchers have primarily measured the perception of pure tone stimuli in mice (Ohlemiller and Gagnon, 2007; Ohlemiller et al., 2010; Prosen et al., 2003); however tones do not accurately represent the sounds heard in a mouse's auditory environment. Mice of both sexes and at most ages produce spectrally and temporally complex vocalizations spanning from low to high frequencies (Ehret and Haack, 1982; Lahvis et al., 2011; Portfors, 2007). Low frequency vocalizations by adult animals are associated with aggressive or defensive behaviors (Lahvis et al., 2011; Portfors, 2007). Furthermore, pups emit low-frequency wriggling calls during mother pup separation (Ehret and Bernecker, 1986). Ultrasonic vocalizations (USVs) are emitted by all adult animals and are thought to be important for acoustic communication, with possible functions such as mate attraction, courtship, and other social interactions (Grimsley et al., 2011; Portfors, 2007; reviewed by Willott, 2001). Male and female mice emit a diverse repertoire of USVs with many different call types, or categories (Ehret, 1992; Ehret and Haack, 1982; Portfors, 2007).

The production of USVs by male mice has been extensively studied. Males generate calling bouts that are composed of several types of USVs arranged in non-random fashion (Chabout et al., 2015; Holy and Guo, 2005; Portfors, 2007). A bout is an organized set of USVs that ranges from 0.5 to 30 s in duration (review by Nyby, 2001). Bouts are thought to be important for mating. Previous research showed that male mice will produce bouts during social interactions with females and males, as well as to female urine, and to anesthetized females and males (Chabout et al., 2015; Hammerschmidt et al., 2009). Chabout et al. (2015) examined how male mice modify their USVs based on social context, finding that they will alter the syllable type, loudness of bouts, and frequency of syllables based on the presence or absence of a female or even just female urine. Therefore, it can be concluded that male mice will adjust the use of their USVs under different situations, suggesting their importance for communication.

USVs vary based on a variety of spectrotemporal parameters, including frequency, amplitude, and duration. Previous researchers have used statistical analyses of spectrograms in order to separate USVs into several categories (Grimsley et al., 2011, 2012; Portfors, 2007). However, it is important to note that the number of categories defined in those studies varies widely, and those categories are not defined by the mouse, but rather by the researchers. Holmstrom et al. (2010) examined whether different USV categories and manipulations of the USV signal elicited different neuronal responses. Inferior colliculus (IC) neurons showed a distinct response for separate USV categories, as well as for altered USVs. Furthermore, Roberts and Portfors (2015) proposed that IC neurons use frequency distortion products to encode the ultrasonic vocalizations. These findings suggest that mice have a distinct neural representation of USVs, possibly not even for the actual frequencies of the vocalizations. Neilans et al. (2014) showed that the CBA/CaJ mouse strain's behavioral ability to discriminate between various vocalizations is based on the spectrotemporal

similarity of the calls, where increased similarity is associated with a decrease in discriminability. Nonetheless, little is known about how mice detect their own USVs, with the effect of aging on the perception of USVs being a particularly understudied phenomenon.

While it is clear that hearing loss in the CBA/CaJ strain resembles human ARHL using pure tones, little is known about how this strain perceives their own vocalizations and even less is known about how aging effects that perception. For the present study, our aim was to establish auditory threshold sensitivity for several USV types, as well as to track these thresholds across the mouse lifespan. The stimuli we used were USVs from six categories outlined in Portfors (2007) and Holmstrom et al. (2010), which included down sweep, up sweep, 30 kHz harmonic, chevron, complex, and male sweep calls, as well as a 42 kHz pure tone. We hypothesized that thresholds would differ across USVs due to differences in spectrotemporal complexity, with the detection of USVs extending into a later age range than pure tones. Further, we expected to see sex differences in USV thresholds, with males having higher thresholds than females, especially at the oldest ages.

2. Methods

2.1. Subjects

The animals used in this experiment were twenty-two adult CBA/CaJ strain mice. Eight subjects (4 males and 4 females) were only used in this experiment. The rest of the subjects (7 males and 7 females) entered the experiment after participating in pure tone behavioral discrimination studies in our laboratory. Training began when the mice were approximately 2–3 months old, and the experiments lasted up to 33 months of age (see results). The original breeding pairs were acquired from The Jackson Laboratory. Our subjects were bred at the University at Buffalo, SUNY, and all procedures were approved by the University at Buffalo, SUNY's Institutional Animal Care and Use Committee. All mice were housed separately and kept on a reverse day/night cycle (lights off at 6 a.m. and lights on at 6 p.m.). Accordingly, the mice were tested during the dark portion of their cycle, 1 h at a time, between 8:00 a.m. and 4:00 p.m. All animals were trained and tested at different hours of the dark portion to establish the hour of best productivity for each individual. Once the schedule was established, mice maintained it throughout their lifetime. They were water restricted and kept at approximately 85% of their free-drinking weights during the course of the experiment. The animals had unrestricted access to food, except while they were participating in the experiments.

2.2. Apparatus

The mice were tested in a wire cage (28 × 56 × 30.5 cm in one of the two setups, and 23 × 39 × 15.5 cm in the other, see Fig. 1) placed in a sound-attenuated chamber (53.5 × 54.5 × 57 cm) lined with 4 cm thick Sonex sound-attenuating foam (Illbruck Inc., Minneapolis, MN). The chamber was illuminated at all times by a small lamp with an 8-W white light bulb, and the behavior of the animals during test sessions was monitored by an overhead web camera (Logitech QuickCam Pro, Model 4000). The test cage consisted of an electrostatic speaker (Tucker-Davis Technologies (TDT), Gainesville, FL, Model ES1), a response dipper (Med Associates Model ENV-302M-UP), and two nose poke holes surrounded by infrared sensors (Med Associates Model ENV-254).

The experiments were controlled by Dell Optiplex 580 computers operating TDT modules and software. Stimuli were sent through an RP2 signal processor, an SA1 power amplifier, a PA5 programmable attenuator, an ED1 electrostatic speaker driver, and finally to the speaker. Inputs to and outputs from the testing cages

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