Short review

The effects of aging on auditory cortical function

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ABSTRACT

Age-related hearing loss is a prominent deficit, afflicting approximately half of the geriatric population. In many cases, the person may have no deficits in detecting sounds, but nonetheless suffers from a reduced ability to understand speech, particularly in a noisy environment. While rodent models have shown that there are a variety of age-related changes throughout the auditory neuraxis, far fewer studies have investigated the effects at the cortical level. Here I review recent evidence from a non-human primate model of age-related hearing loss at the level of the core (primary auditory cortex, A1) and belt (caudolateral field, CL) in young and aged animals with normal detection thresholds. The findings are that there is an increase in both the spontaneous and driven activity, an increase in spatial tuning, and a reduction in the temporal fidelity of the response in aged animals. These results are consistent with an age-related imbalance of excitation and inhibition in the auditory cortex. These spatial and temporal processing deficits could underlie the major complaint of geriatrics, that it is difficult to understand speech in noise.

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As the human population continues to grow older, age-related illnesses and deficits are becoming increasingly common and economically pressing. A major class of deficits are in sensory processing, particularly hearing, which afflicts over half of the geriatric population. These deficits can lead to social isolation, depression, and have been correlated with a variety of cognitive deficits (Humes et al., 2012; Sung et al., 2016; Huddle et al., 2017; Loughrey et al., 2017). Thus, it is imperative to better understand how aging affects the peripheral and central nervous systems, giving rise to these perceptual deficits.

Historically, age-related hearing loss was largely attributed to the periphery, with various types of hearing loss related to different structural and anatomical deficits in the cochlea (Schuknecht, 1955, 1964; Ramadan and Schuknecht, 1989; Schuknecht and Gacek, 1993; see Engle et al., 2013). More recently it has become clear that, even in individuals with normal detection thresholds, they can still suffer age-related hearing *deficits*. For those afflicted, these deficits are generally manifest as a reduced ability to understand speech, particularly in noisy environments (i.e. Snell et al., 2002; Alain et al., 2014; Füllgrabe et al., 2014). As social settings are often in noisy environments (i.e. restaurants, parties, etc.), challenges facing geriatrics to have meaningful interactions in these

environments can be overwhelming, potentially giving rise to the social isolation that is commonly seen in age-related hearing loss (Humes et al., 2012; Sung et al., 2016; Huddle et al., 2017). In the laboratory, aged individuals show both spatial and temporal processing deficits, even when they either have normal hearing thresholds or the specific stimuli are matched in loudness to younger subjects (e.g. Brown, 1984; Frisina and Frisina, 1997; Abel et al., 2000; Snell et al., 2002; Gordon-Salant and Fitzgibbons, 2001; Gordon-Salant et al., 2006; Humes et al., 2009; Dobreva et al., 2011; Füllgrabe et al., 2014; Freigang et al., 2015). This makes intuitive sense, as one needs to identify the location of the talker of interest (spatial processing) as well as the different segments and parameters of the speech signal itself (temporal processing). Given the complexity of the deficits, even in individuals with normal detection thresholds, much of the deficits must be central in origin, implying that there are age-related changes in how the nervous system processes both spatial and temporal auditory information. In addition to these sensory processing deficits, there are clearly established age-related cognitive deficits as well, particularly with respect to attention (e.g. Anthony and Lin, 2017; Lehert et al., 2015; Kelly et al., 2014). While it is very difficult to disentangle the interactions between bottom-up sensory processing and top-down cognitive control, this review will focus on the sensory processing aspects of age-related hearing deficits, and summarize some recent experiments in both rodent and non-

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human primate models that are beginning to reveal how aging affects general cortical processing.

1. Age-related changes in cortical activity: spatial processing

Recent studies in the macaque and rat have indicated that there are clear aging effects in the auditory cortex that are consistent with the age-related hearing deficits noted above in humans, most notably in sound location processing and in temporal processing. The macaque monkey has proven to be an excellent animal model for cortical function, and this species ages at about 3X that of the human (Davis and Leathers, 1985), so monkeys on the order of 20 + years are considered geriatric. The macaque also has a similar hearing range as for humans, particularly in the lower frequency range, which is inaudible in rats and mice (Fig. 1A). The primate auditory cortex, including humans and macaques, is made up of a core region composed of three cortical areas (Kaas and Hackett, 2000; Hackett et al., 2001): the primary auditory cortex (A1), the rostral field (R) and the rostro-temporal field (RT). Surrounding the core are several belt fields, including the caudolateral field (CL), appropriately named as it is located caudal and lateral to the core area. The working hypothesis is that there are different auditory streams processing spatial (the caudal stream) and non-spatial (the rostral stream), which was originally put forth by Rauschecker (1998) and has framed many subsequent experiments in both humans and animal models (see Rauschecker, 2017). Direct evidence in favor of a spatial processing stream in non-human primates comes from the finding that neurons in CL have sharper spatial tuning than other core and belt fields (Woods et al., 2006), and the firing rate of those neurons can account for human sound localization ability (Miller and

Recanzone, 2009). The observation that there are age-related sound localization deficits (Abel et al., 2000; Ross et al., 2007; Dobreva et al., 2011; Freigang et al., 2015) suggests that the aging process would particularly affect neurons in CL.

A series of studies have been conducted in two aged macaques (aged ~25 years) that had normal behaviorally-measured audiograms, so any deficits seen could not be attributed to a decline in auditory sensitivity (Fig. 1B; Juarez-Salinas et al., 2010). The initial observations on the effects of aging of A1 and CL neurons were that there is an increase in both spontaneous and driven activity (Fig. 2; ANOVA all p < 0.01; Juarez-Salinas et al., 2010; Engle and Recanzone, 2012; Ng and Recanzone, 2017). While this may initially seem surprising, it is consistent with numerous histochemical and histopathological changes that have been noted in both rat and monkey models throughout the auditory neuraxis from the cochlea through the brainstem and midbrain and up to the thalamus. These changes are consistent with a decrease in inhibition, presumably in response to the decreased drive from the cochlea (see Caspary et al., 2008; Ouda et al., 2015; Gray and Recanzone, 2017). These histochemical changes are seen in both the medial and lateral geniculate nuclei (auditory and visual relay nuclei, respectively), but to a greater extent in the auditory thalamus (Gray et al., 2013). Thus, it is not surprising that changes in both spontaneous and driven rates are also seen in visual cortical areas V1 and MT of anesthetized aged macaque monkeys (Schmolesky et al., 2000; Yu et al., 2006; Yang et al., 2008; Zhang et al., 2008; Liang et al., 2010; see also Mendelson and Wells, 2002). In the visual studies, there was a decrease in the signal to noise ratio, where the driven response was not as much greater than the spontaneous rate compared to younger animals. In auditory cortical areas A1 and CL the signal to noise ratio was higher in the aged animals, indicating that the increased driven rate in the aged animals was relatively greater than in the younger animals.

The visual studies also noted that the orientation tuning and direction selectivity was poorer for the aged neurons compared to the younger ones. A similar finding was made in the auditory cortex of aged macaques, where the spatial tuning was greater in the aged neurons compared to the younger ones (Juarez-Salinas et al., 2010; Engle and Recanzone, 2012). The results are shown in Fig. 3, where A1 neurons are shown in closed bars and CL neurons are shown in open bars. Across the population of young neurons, there was relatively broad tuning in A1, which was sharpened in CL neurons, as indicated by an increase in the vector strength, a metric of tuning in circular distributions (Fig. 3A). This was in stark contrast to neurons in aged monkeys. While there was relatively broad tuning in A1 as in the younger monkeys (Fig. 3B), the distribution of the tuning index was essentially identical in CL to that in A1 (open vs. closed bars in Fig. 3B). Thus, the sharpening of tuning between A1 and CL in younger animals, which could account for sound localization ability (Miller and Recanzone, 2009), was lost in the aged animals.

There were also two differences between young and aged neuronal responses in the latency of the first action potential. First, the latency for aged neurons was statistically significantly shorter than those for young neurons (Engle and Recanzone, 2012), with mean first spike latencies in A1 of ~17 msec in young monkeys and ~14 msec in aged monkeys. This finding is consistent with that seen in the rodent inferior colliculus (Simon et al., 2004). This difference was even greater in CL, where there was a statistically significant increase between A1 and CL in young monkeys (to ~20 msec), but no difference between A1 and CL in the aged monkeys (CL also ~14 msec). The second difference is the change in latency as a function of spatial location. In young monkeys, the shortest latency responses for A1 neurons was for stimuli at the best location (defined as the location with the greatest response), with latencies increasing with increasing distance from the best location, with a
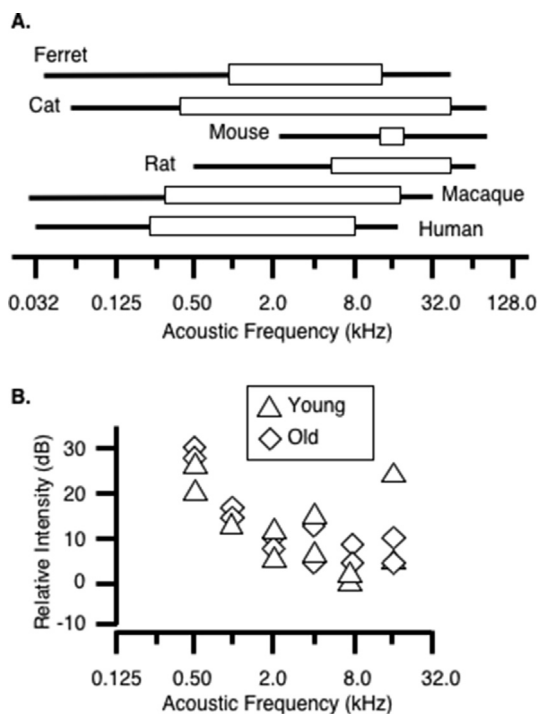

Fig. 1. Hearing range for humans and common laboratory animals. A. The solid lines show the frequency span with detection thresholds of 60 dB SPL or lower. The rectangles show the frequency span with detection thresholds of 10 dB SPL or lower. Data for ferrets taken from Kelly et al. (1986). Data for all other species taken from Heffner and Heffner (2007). B. Detection thresholds for the two aged animals (diamonds) described in this review compared to two young controls (triangles). The aged animals had normal detection thresholds measured relative to the lowest threshold measured by the youngest monkey. Data taken Juarez-Salinas et al., 2010.