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## 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; Dobrev 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; Leher 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

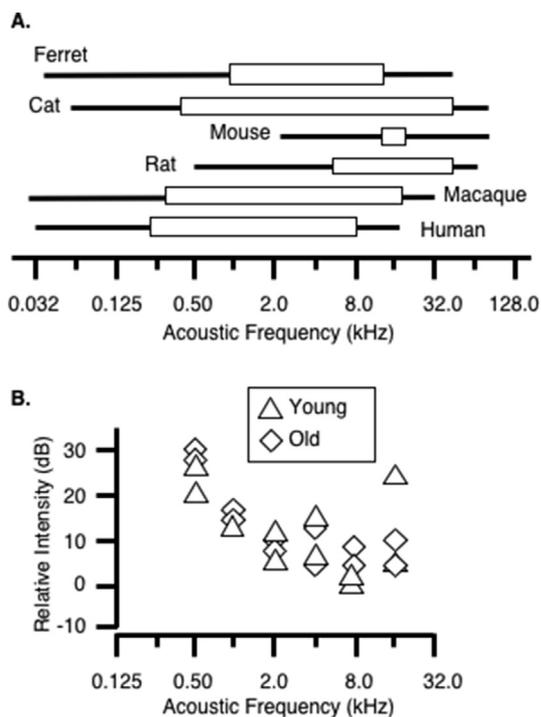
Recent studies in the macaque and rat have indicated that there are clear aging effects in the auditory cortex that are consistent with the age-related hearing deficits noted above in humans, most notably in sound location processing and in temporal processing. The macaque monkey has proven to be an 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; Dobрева et al., 2011; Freigang et al., 2015) suggests that the aging process would particularly affect neurons in CL.

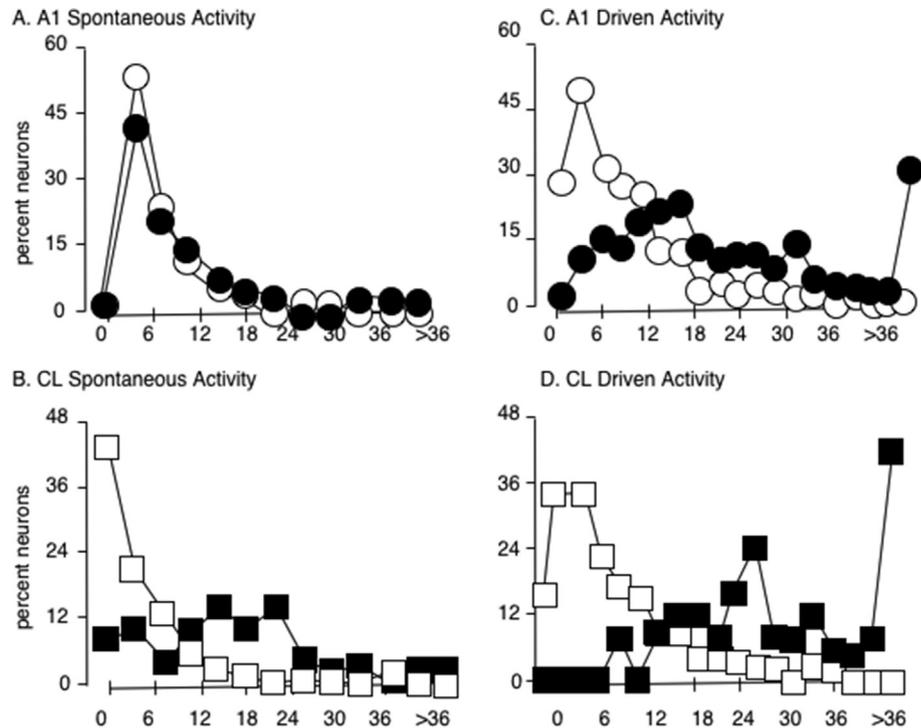
A series of studies have been conducted in two aged macaques (aged ~25 years) that had normal behaviorally-measured audiograms, so any deficits seen could not be attributed to a decline in auditory sensitivity (Fig. 1B; Juarez-Salinas et al., 2010). The initial observations on the effects of aging of 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.



**Fig. 2.** Aged neurons have higher spontaneous and driven firing rates in auditory cortex. A. Distribution of spontaneous activity in A1 neurons. Aged animals (black circles) have significantly higher spontaneous activity compared to young animals (open circles). B. Distribution of spontaneous activity in CL neurons. Similar to A1, CL neuron in aged animals (black squares) had higher spontaneous activity compared to young animals (open squares). C. Distribution of driven firing rates in A1. Distribution of firing rates of neurons to a 200 msec duration broadband noise burst from the location that elicited the greatest response. Aged neurons showed greater driven firing rates compared to younger neurons. D. Distribution of driven firing rates in CL. Again, aged neurons had greater firing rates than young neurons. Conventions in C and D the same as in A and B, respectively. Error bars are smaller than the symbol size. Data taken from [Juarez-Salinas et al., 2010](#).

difference of 1–2 msec between the best and opposite locations. This difference was even greater in CL neurons of young monkeys, with latencies on the order of ~4 msec longer at the location opposite to the best direction (see [Engle and Recanzone, 2012](#) for details). In contrast, in both A1 and CL in the aged animals, there was no difference either between cortical areas as noted above, or between the best and opposite locations (all ~14 msec).

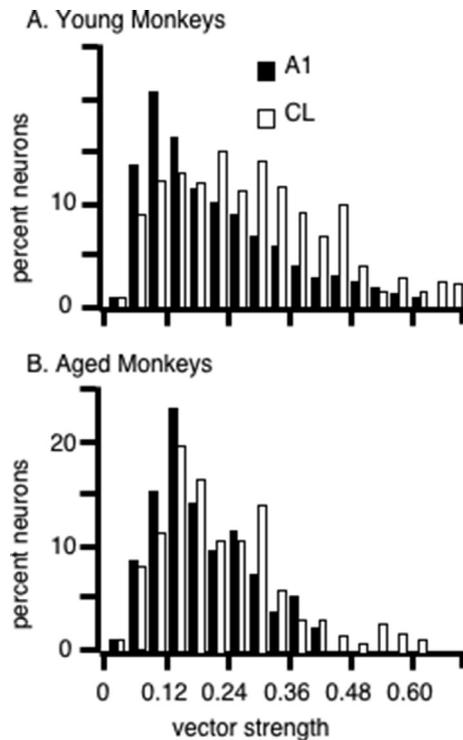
These changes in spatial tuning between young and aged neurons in areas A1 and CL are consistent with the hypothesis that aging results in a change in the balance of excitation and inhibition. As noted above, there is abundant evidence that histochemical changes in the cochlea are consistent with a decreased excitatory drive into the brainstem (see [Engle et al., 2013](#); [Valero et al., 2017](#)), and there are a series of compensatory mechanism throughout the ascending auditory neuraxis. The cortex necessarily inherits these changes, and as such, it is not surprising that there is an increase in both spontaneous and driven activity. These results also show that this balance of excitation and inhibition is critical for the normal sharpening of at least spatial tuning, particularly between cortical areas A1 and CL. The short latencies between A1 and CL indicate that in aged monkeys, there is little influence, at least at stimulus onset, of CL neuronal responses by A1 neurons that are normally occurring in younger animals. This would clearly disrupt the normal hierarchical cortical processing and could underlie, at least in part, the spatial processing deficits seen in aged individuals.

## 2. Age-related changes in cortical activity: temporal processing

The second common age-related hearing deficit is in temporal processing, such as gap detection ([Gordon-Salant et al., 2006](#);

[Humes et al., 2009](#); [Palmer and Musiek, 2014](#); [Ozmeral et al., 2016](#)), potentially underlying the deficits in speech processing, particularly in background noise (e.g. [Frisina and Frisina, 1997](#); [Gordon-Salant and Fitzgibbons, 2001](#); [Snell et al., 2002](#); [Füllgrabe et al., 2014](#)). Temporal processing changes have been noted in rodent inferior colliculus ([Barsz et al., 2002](#); [Allen et al., 2003](#); [Walton, 2010](#)) as well as the auditory cortex ([Mendelson and Ricketts, 2001](#)) however, very little has been investigated at the level of the auditory cortex. A recent study in non-human primates has compared the responses to amplitude modulated (AM) broadband noise in the primary auditory cortex of aged passively listening monkeys with normal behavioral audiograms ([Overton and Recanzone, 2016](#)) and compared those responses to those of younger monkeys from a different study ([Yin et al., 2011](#)). There are several simple ways that the responses of single neurons could underlie temporal processing deficits in aged individuals. The first is by a decrease in the number of neurons that are responsive to temporally modulated stimuli, the second is by a change in the coding strategy across the population of neurons, and a third is by a decrease in the temporal fidelity, or temporal tuning, of the responses. None of these are mutually exclusive, and one or all three could be in play with normal aging. In order to address the first possibility, the percentage of neurons that were significantly responsive to AM stimuli across a broad range of modulation frequencies were compared between young and aged animals. The results showed no difference in the overall number of neurons that show statistically significant responses to such stimuli ([Overton and Recanzone, 2016](#)). Thus, a simple decrease in tuned neurons cannot account for these age-related deficits.

The second possibility was also tested, that there could be a change in the coding strategy by the different neurons, and there



**Fig. 3.** Spatial tuning increases from A1 to CL in young, but not aged monkeys. A. Distributions of the vector strengths for A1 (solid bars) and CL (open bars) for neurons in young monkeys. There is a clear increase in vector strength in CL neurons, indicating sharper spatial tuning. B. The same distribution for aged monkeys. In this case, CL neurons have a similar distribution of vector strengths, indicating that there is not a sharpening of tuning between these cortical areas. Data taken from [Juarez-Salinas et al., 2010](#).

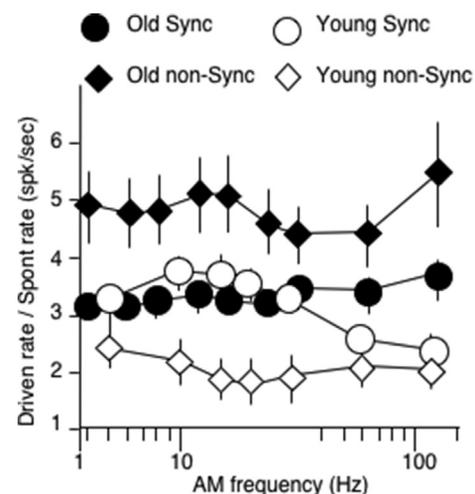
was a significant difference in the types of temporal coding strategies that were used between young and aged animals. There are at least two primary ways that a neuron can represent temporally modulated stimuli. One is a firing rate code, where the overall spike rate varies as a function of modulation frequency. The second is a temporal code, where the timing of the spikes has a consistent temporal relationship with the envelope of the stimulus. When comparing the percentages of neurons with different tuning strategies, with young monkeys having more neurons with significant responses using both a temporal and firing rate code, and older monkeys having fewer neurons that responded using both codes but more that used only a firing rate code. Thus, there appears to be a shift in coding strategy between temporal coding versus rate coding of these temporally dynamic stimuli.

To investigate whether there was also a change in the temporal fidelity of those neurons that continue to use a temporal code in aged monkeys, the phase-projected vector strength was tested for those neurons that had significant temporal responses in both sets of monkeys ([Yin et al., 2011](#); [Overton and Recanzone, 2016](#)). The findings were that there was an overall decrease in the vector strength values in the aged monkeys compared to the younger monkeys, indicating that not only are fewer neurons providing temporal envelope information in the aged monkeys, but also that the envelope information is not as good in the aged animals as in the younger animals.

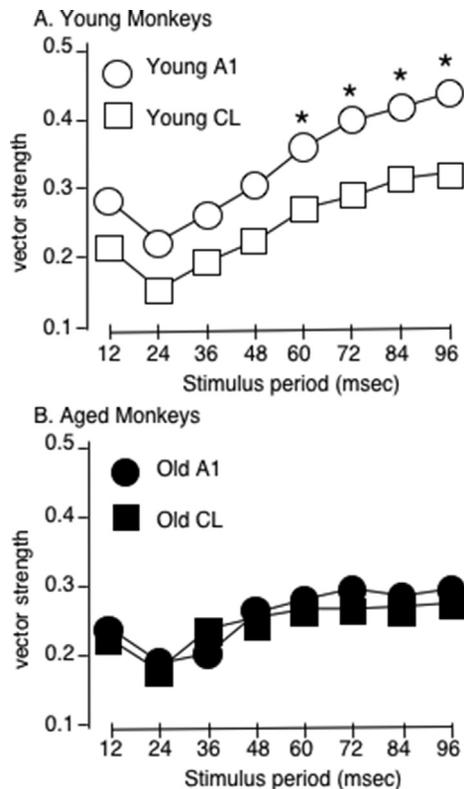
Finally, a comparison was also made with respect to the firing rates of neurons that either responded significantly by both a temporal code as well as a firing rate code (synchronous cells) compared to those that were only sensitive with a firing rate code

(non-synchronous). The results of this analysis showed a rather surprising result ([Fig. 4](#)). For the synchronous cells, the firing rates were equivalent between the young and aged neurons (open and filled circles, respectively). This is in contrast to the previous finding that aged neurons have higher driven firing rates compared to their spontaneous activity compared to younger neurons when responding to unmodulated broadband noise stimuli ([Juarez-Salinas et al., 2010](#)). However, when comparing the firing rates for the non-synchronous cells in young and aged neurons (open and filled diamonds, respectively) there is a dramatic increase in the absolute and relative firing rates in the aged neurons. This, coupled with the larger percentage of neurons that are responsive in a non-synchronous manner, is consistent with the overall increased firing rate seen in the previous studies to the unmodulated noise stimuli. Additionally, it indicates that there is a clear break in the neuronal coding strategy between young and aged neurons. The aged neurons essentially abandon an envelope encoding strategy, and instead of reducing their overall firing rate to provide more dynamic range in encoding different AM frequencies, the firing rate is increased.

A second series of studies in these same aged animals, using discrete tone pips and noise bursts, showed similar results between young and aged animals. Importantly, this study compared both A1 and CL neurons, similar to the spatial response studies described above. When comparing the vector strengths of young and old neurons as a function of the stimulus/inter-stimulus interval period, there was a clear difference between A1 and CL neurons in young animals ([Fig. 5A](#)) with significant differences at the longer periods (lower frequencies; [Ng and Recanzone, 2017](#)). This is consistent with the notion that CL neurons process spatial information in favor of temporal information, and thus it is not expected that they should necessarily carry forward the temporal coding of the A1 neurons. When considering the aged animals, however, there was no difference between A1 and CL. Importantly, it is not that CL neurons had better temporal precision, rather, the aged A1 neurons were equivalent to both the aged and young CL neurons



**Fig. 4.** Aged monkeys have similar firing rates for synchronized cells, but higher firing rates for non-synchronized cells. Synchronized cells (circles) were defined as having statistically significant vector strength to at least one of the amplitude modulated noise stimuli tested. Non-synchronized cells (diamonds) did not have statistically significant vector strength, but did have a statistically significant firing rate above spontaneous for at least one tested stimulus. Firing rates are normalized by the spontaneous activity. For synchronous cells, the firing rates were on the order of 3–4X the spontaneous activity for both young (open circles) and aged (black circles) neurons. For non-synchronous cells, the firing rate for the aged neurons (black diamonds) had a several-fold higher average firing rate compared to younger neurons (open diamonds). Data taken from [Overton and Recanzone, 2016](#).



**Fig. 5.** Vector strength is greater for neurons in A1 than CL for young, but not aged monkeys. A. Average vector strength as a function of the tone-pip + inter-pip-interval of the presented sequences in young monkeys. Stimuli consisted of 4 tone pips with equal pip duration and intervals, at the characteristic frequency of the tested cell. A1 neurons (circles) had higher vector strengths overall, indicating better temporal fidelity in representing the envelope of the stimulus. Statistical significance was seen for the longest duration stimuli (lower temporal rates) comparing A1 to CL neurons (asterisks indicate  $p < 0.05$ ). B. Average vector strengths in aged monkeys. In these animals, the vector strengths of the CL neurons were equivalent to those in the younger monkeys (compare open and closed squares in A and B, respectively). However, the vector strengths in A1 neurons were equivalent to those of CL neurons in the aged animals. Data taken from Ng and Recanzone, 2017.

(Fig. 5B). Thus, the temporal fidelity of the A1 responses in aged animals is not enhanced as compared to area CL, which is not believed to be critical for temporal processing.

### 3. Age-related changes in cortical activity: conclusions

Experiments on both spatial and temporal processing in macaque monkeys, reviewed above, indicate that there is a dramatic change in activity, tuning, and coding strategies of auditory cortical neurons as a function of age. These changes are primarily age-related, as these aged animals had normal behaviorally measured audiograms and would be considered to have 'normal hearing' by most audiologists. Unfortunately, perceptual studies were not possible in these animals so their potential spatial and temporal processing deficits could not be defined.

One question that arises is how much of these changes are inherited from sub-cortical areas. Studies in both animal models (reviewed in Kujawa and Liberman, 2015), macaque monkeys (Engle et al., 2013; Valero et al., 2017) and humans (Viana et al., 2015) indicate that synaptic loss at the level of the inner hair cells precedes actual hair cell loss, giving rise to 'hidden hearing loss'. This would lead to a decreased afferent drive from the cochlea, which could give rise to the histological changes throughout the ascending auditory system (see Caspary et al., 2008; Ouda et al.,

2015; Gray and Recanzone, 2017) but not necessarily changes in detection thresholds. Electrophysiological studies have shown decreases in the temporal fidelity of frequency following responses in the auditory brainstem responses in old compared to young rats (Parthasarathy et al., 2014), and similarly reduced temporal fidelity has been noted in both the brainstem and cortical level in humans (Vander Werff and Burns, 2011; Ozmeral et al., 2016), so it is likely that a great deal of the measured cortical responses are inherited. However, it should be noted that some of these differences must be cortical in nature. For example, the increased sharpness of spatial tuning and response latencies between A1 and CL in young monkeys was lost in the older monkeys. These data indicate that the transformation of information along the cortical hierarchy is clearly affected as well.

The results described in the monkeys are consistent with electrophysiological and functional imaging studies in humans as well. For example, it has been noted that there is generally a decrease in the magnitudes of different peaks in the neuro-magnetic signal in aged vs. younger individuals (McDonald and Alain, 2005). This is consistent with a decreased synchrony of the neural responses, such as decreased phase-projected vector strength and temporal processing in both A1 and CL of aged monkeys. Similar decreases in temporal fidelity have been noted as a function of interaural timing differences, an important cue for sound localization (Ozmeral et al., 2016). Such neurophysiological deficits could account for the psychophysical deficits observed in aging humans in both temporal and spatial processing (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).

Finally, it should be noted that the monkeys in the studies reviewed here were passively listening to these sounds, and neither of the aged animals had been trained at any sort of auditory task. It could be that actively engaging the subject, animal or human, in discriminating specific auditory sounds could restore normal cortical function. For example, studies in rats have compared age-related changes in auditory cortical processing as well as perceptual abilities on a temporally based task (deVilliers-Sidani et al., 2010). The monkey results are consistent with those findings, but that series of studies had two additional findings. The first is that there was an increase in the number of neurons expressing somatostatin, which was interpreted to indicate that there was a change in GABAergic inhibition in the aged animals, consistent with previous anatomical studies. Importantly, both the physiological responses and anatomical changes were reversed in animals that underwent a training period, indicating that these central changes are not permanent. This finding is consistent with human auditory training paradigms, where different listening tasks can result in both improvements in auditory temporal processing tasks as well as the electrophysiological correlates of brainstem and midbrain responses (Anderson et al., 2013, 2014; Merzenich et al., 2014; Cheng et al., 2017). Thus, while aging can result in rather dramatic physiological and neuroanatomical changes throughout the central nervous system, these particular changes, at least to some degree, appear to be plastic and malleable throughout life. The key questions, then, are what particular aspects of both the physiological changes as well as the training paradigms will be most efficient for preventing and/or reversing age-related hearing deficits.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.heares.2018.05.013>.

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