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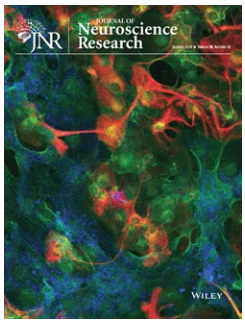
RESEARCH ARTICLE



Evidence for independent peripheral and central age-related hearing impairment

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Abstract

Deleterious age-related changes in the central auditory nervous system have been referred to as central age-related hearing impairment (ARHI) or central presbycusis. Central ARHI is often assumed to be the consequence of peripheral ARHI. However, it is possible that certain aspects of central ARHI are independent from peripheral ARHI. A confirmation of this possibility could lead to significant improvements in current rehabilitation practices. The major difficulty in addressing this issue arises from confounding factors, such as other age-related changes in both the cochlea and central non-auditory brain structures. Because gap detection is a common measure of central auditory temporal processing, and gap detection thresholds are less influenced by changes in other brain functions such as learning and memory, we investigated the potential relationship between age-related peripheral hearing loss (i.e., audiograms) and age-related changes in gap detection. Consistent with previous studies, a significant difference was found for gap detection thresholds between young and older adults. However, among older adults, no significant associations were observed between gap detection ability and several other independent variables including the pure tone audiogram average, the Wechsler Adult Intelligence Scale-Vocabulary score, gender, and age. Statistical analyses showed little or no contributions from these independent variables to gap detection thresholds. Thus, our data indicate that age-related decline in central temporal processing is largely independent of peripheral ARHI.

KEYWORDS

age-related hearing impairment, central presbycusis, peripheral hearing loss, temporal processing

1 | INTRODUCTION

Age-related hearing impairment (ARHI) is the most common neurodegenerative disease, afflicting over 70% of the U.S. population over 85 years of age (Frisina, Mapes, Kim, Frisina, & Frisina, 2006; Parham, Lin, Coelho, Sataloff, & Gates, 2013). Traditionally, ARHI has been considered the result of deleterious changes in only the auditory periphery, including the middle ear, cochlear hair cells, and

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acoustic nerve fibers, as evidenced by reduced threshold sensitivity on the pure tone audiogram. The use of the diagnostic term presbycusis ("elderly hearing") to refer to ARHI reflects the common assumption that the speech processing difficulties of older persons should be predictable from their cochlear audiometric configuration (Pacala & Yueh, 2012; Schuknecht & Gacek, 1993). However, clinical interventions aimed at compensating for peripheral hearing loss (e.g., hearing aids) often do not provide adequate benefit for many older patients, suggesting that peripheral and central ARHI are distinct conditions (Gates, 2012; Harris & Dubno, 2017). In humans, however, it is difficult in practice to disentangle the possible interactions between auditory sensory processing and cognitive influences (American Academy Of Audiology, 2010; Humes et al., 2009, 2012, 2013; Recanzone, 2018).

Peripheral ARHI was historically assumed to be due to age-related loss of cochlear hair cells, which led to age-related loss of spiral ganglion neurons (SGNs). However, our studies have shown that normal age-related loss of hair cells, SGNs, and cochlear synapses between outer hair cells and medial olivocochlear efferent fibers can occur independently (Fu et al., 2010; Jin et al., 2011). Thus, it is possible that at least some aspects of central ARHI are independent from peripheral ARHI. Despite the clinical evidence and strong animal data favoring the existence of central ARHI (Parham et al., 2013; Recanzone, 2018; Tyler, Summerfield, Wood, & Fernandes, 1982), one extensive review of over 165 research papers focusing on this topic concluded that "there is insufficient evidence to confirm the existence of central presbycusis as an isolated entity." (Humes et al., 2012). The main reason is most likely due to comorbidity and the difficulties in disassociating central ARHI from age-related declines in other brain functions such as memory loss. The gap detection threshold (GDT) has been established as the single most common measure of central auditory temporal processing because cognitive influence is minimal, making gap detection potentially ideal for disentangling peripheral and central ARHI (Creelman, 1962; Divenyi & Hirsch, 1974; Preece & Tyler, 1989; Gordon-Salant & Fitzgibbons, 1999; Frisina, 2001; Schoof & Rosen, 2014). Subsequent studies have clearly demonstrated longer GDTs in older populations (Harris & Dubno, 2017; Ozmeral, Eddins, Frisina, & Eddins, 2016; Palmer & Musiek, 2014). However, the question of whether central ARHI could exist independently of peripheral hearing loss remains to be addressed. Although a few previous studies have found no influence of cognitive factors on GDTs (e.g., Schoof & Rosen, 2014), further studies are needed to determine if different cognitive aspects may influence GDTs. Furthermore, audiometric threshold measurements, which are typically performed to monitor peripheral ARHI, lack the sensitivity to detect cochlear pathology. For example, hearing thresholds show little change until SGN loss exceeds about 80%–90% (Schuknecht & Woellner, 1955). Recent work in animal models has clearly established the concept of hidden hearing loss, at least for noise-induced hearing loss, whereby animals with normal hearing thresholds have widespread cochlear synaptopathy of small SGN afferent fibers with intact hair cell populations (Kujawa & Liberman, 2019). Interestingly, the use of high-frequency audiograms (up to 16 kHz) may be useful to monitor hidden hearing loss in humans (Liberman, Epstein, Cleveland, Wang, & Maison, 2016). In addition, there is a clear inverse relationship between the noise bandwidth used for gap detection and GDTs (e.g., Ozmeral et al., 2016; Snell, Ison, & Frisina, 1994). In almost all previous studies, however, audiograms measuring only to 4 or 8 kHz were used to examine associations between peripheral and central presbycusis (Humes et al., 2012). Therefore, it is important to also investigate whether age-related peripheral hearing loss in higher frequencies contributes to age-related decline of auditory temporal processing.

To address whether central ARHI is associated with peripheral ARHI, here we examined possible associations between GDT and pure tone hearing thresholds with consideration of other factors such as age, gender, and performance on the Wechsler Adult Intelligence Scale (WAIS-IV). To reduce complications such as age-related declines in attention and processing speed, we adopted a gap detection method that utilizes a fixed gap location in the center of the sound trial (Harris, Eckert, Ahlstrom, & Dubno, 2010). To investigate the possible influence of cognitive function on gap detection, the WAIS-IV, an established measure of working memory and cognitive function (Gennis, Garry, Haaland, Yeo, & Goodwin, 1991; Wisdom, Wignogna, & Collins, 2012) was administered and compared to GDTs for tentative associations. In addition, we extended threshold testing beyond standard audiometric frequencies to include higher frequencies. Collectively, this study aimed to determine if peripheral and central ARHI are independent variables for this condition.

Significance

Based on extensive statistical analyses, our study supports a new concept that central age-related hearing impairment (ARHI) could exist largely independent of peripheral ARHI during aging. Beyond the basic scientific significance of revealing independent aging processes in different parts of the nervous system, our findings suggest a need to revise current clinical thinking regarding ARHI, implement differential testing to separate central presbycusis from peripheral hearing loss, and design appropriate auditory rehabilitative strategies focused on central ARHI.

2 | METHODS

2.1 | Ethical approval for human study

All procedures performed in studies involving human participants were in accordance with the revised version of the Declaration of Helsinki and approved by the Institutional Review Board for Protection of Human Subjects of Washington University in St. Louis (WUSTL) and Northeast Ohio Medical University (NEOMED).

2.2 | Participants

A total of 181 subjects were recruited at two sites: 167 subjects were recruited at WUSTL, which included 44 young adults (31 females; 13 males) ranging in age from 18–26 years and 123 older adults (78 females; 45 males) ranging in age from 43–91. In addition, a total of 14 older adults (10 females; 4 males) ranging in age from 57–79 years were recruited at NEOMED. All participants provided informed consent for their inclusion in the study and were compensated for their participation. Exclusionary criteria for both sites were established by means of a questionnaire, results of the Mini Mental State Exam (a score of ≤25; MMSE; Folstein, Folstein, & McHugh, 1975), otoscopic and tympanometric findings. The exclusionary criteria on the questionnaire included: history of severe head injury, middle ear disease, multiple sclerosis, peripheral neuropathy, dementia, stroke, and seizure.

2.3 | Measurements

2.3.1 | Audiometric assessment

All participants completed a standard clinical audiometric assessment including pure tone, air conduction thresholds (0.25, 0.5, 1, 2, and 4 kHz), and tympanometry to assess middle ear function. These audiometric data were used to calculate pure tone averages (PTAs), which refers to the average of hearing threshold levels at a set of specified frequencies. For the data from WUSTL, two PTAs were obtained; PTA-L, an average of low-frequency hearing thresholds at 0.25, 0.5, and 1 kHz; and PTA-H, an average of higher frequency hearing thresholds at 2 and 4 kHz. Because age-related hearing loss typically starts at higher audiometric frequencies and these higher frequencies (6–16 kHz) may be a more sensitive indication of hidden hearing loss (Liberman et al., 2016), measurements from our second cohort at the NEOMED site included hearing thresholds for higher audiometric frequencies, which are not commonly measured during standard clinical testing. Additional PTAs from this cohort were obtained as PTA-UH, an average of hearing thresholds at upper high frequencies of 6, 8, and 10 kHz, and PTA-UH2, an average of hearing thresholds at very high frequencies of 12.5, 14, and 16 kHz.

2.3.2 | Cognitive evaluation

To assess possible effects of working memory on GDTs, we administered the vocabulary subtest of the WAIS-IV to all participants (n = 81; 28 males; 53 females) at the WUSTL site. The vocabulary subtest consists of digit span forward, digit span backward, digit span sequencing, and letter number sequencing tasks.

2.3.3 | GDTs

All participants completed the same gap detection test presented monaurally to the ear with better audiometric thresholds. The protocol for this task was modeled after that of Humes, Busey, Craig, and Kewley-Port (2009), Humes, Kewley-Port, Fogerty, and Kinney (2010), which consisted of three threshold estimates, plus a training session. Each estimate was determined by means of a tracking procedure that employed a three-interval, two-alternative, forced-choice response protocol. On each trial, the participant was presented three 1.5 kHz-wide bands of noise, centered at 1.5 kHz, that were 400 ms in duration and separated by 400 ms of silence. The center frequency at 1.5 kHz is defined as the geometric mean of the upper and lower frequencies of the band (the middle of the band using a logarithmic scale). The sound level was set at 55 decibels normalized hearing level (dB nHL). The first interval never had a gap and was considered the reference interval. A silent gap of varying duration was randomly assigned to the center of one of the remaining two intervals, and participants were instructed to select the interval which contained the brief silent gap. GDTs were determined by an adaptive, up-down staircase tracking procedure that estimated the smallest gap duration that could be detected 70.7% of the time (Levitt, 1970). Beginning with larger gap durations, the gap duration decreased each time a participant identified the interval with the gap correctly twice in a row and increased each time the participant was incorrect. A 4 ms step size was used for trials within the first four reversal points, and a 2 ms step size was used for trials within the last five reversal points. Threshold estimates for each run were taken as the average of the last six reversal points, and the final threshold was an average of the three runs. Stimuli were generated

TABLE 1 WUSTL participant characteristics and test performance

	Young	Older
Number	44	112
Age range	18–26	43–91
Average age	20.9 ± 2.0	70.6 ± 7.0
Gender (F/M)	31 F, 13 M	78 F, 34 M
PTA-L (dB HL)	3.0 ± 5.3	19.9 ± 12.8
PTA-H (dB HL)	1.5 ± 4.2	31.3 ± 16.7
WAIS	54.6 ± 5.0	48.8 ± 9.2
GDT (ms)	8.84 ± 4.0	12.71 ± 14.0

Abbreviations: GDT, gap detection threshold; PTA-H, pure tone average high frequency (2,000 and 4,000 Hz); PTA-L, pure tone average low frequency (250, 500, and 1,000 Hz); WAIS-IV, Wechsler Adult Intelligence Scale fourth edition Vocabulary subtest; ± followed by standard deviation.

using a TDT-RP2.2 processor controlled by PC software written in LabVIEW® to manage presentation parameters and the experimental flow. All audio from the RP2.2 and headphone buffer were routed to insert earphones through an audiometer (GSI-16).

2.4 | Data analysis

Data analyses were performed using either SAS (version 9.2), SPSS (version 22.0), or R (version 3.5.2). First, to assess the differences in GDTs between different groups, unequal sample size and unequal variance *t* tests were used to compare GDT between young and elderly, and between elderly with good hearing (GE; PTA-L < 20 dB HL) and elderly with hearing loss (No_GE; PTA-L > 20 dB HL). Second, three models of linear regression analysis (model 1, model 1 nested in model 2, and model 2 nested in model 3) were performed to study possible associations between GDTs with age, gender, cognitive score and PTA. The marginal association between GDT and age was first tested and then by adding more covariates, we investigated how much gender, cognitive

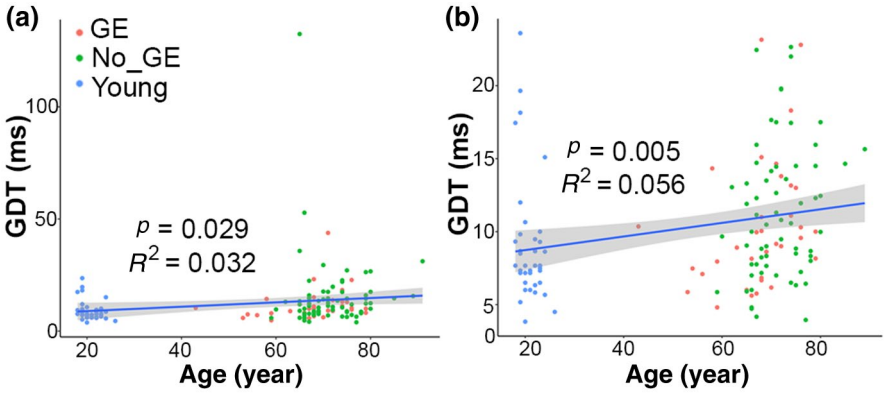

FIGURE 1 Data distribution for GDTs and age among young and older adult groups. (a) All GDT data were calculated and illustrated for the three groups. (b) All GDT data were calculated and illustrated except nine outliers from older adult groups. The scale level for this panel is smaller compared to the level of Panel A. A significant association between GDT and age was observed

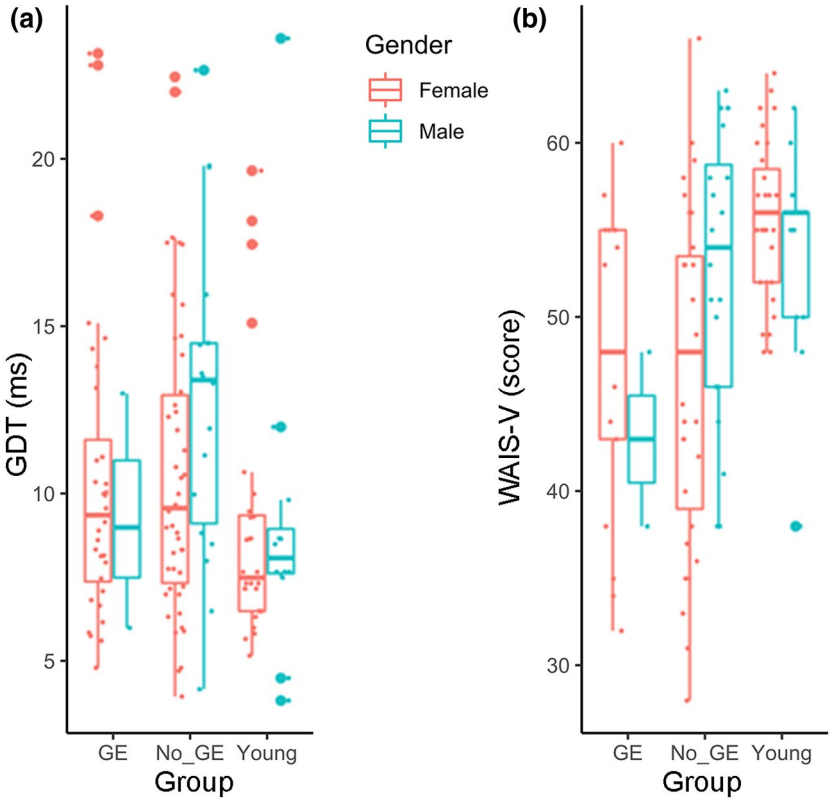

FIGURE 2 Data distribution for GDTs and WAIS-V scores among young and older adult groups. (a) All GDT data except nine outliers were calculated and illustrated. Outliers (outside the first and third quartiles) were plotted as individual larger points. (b) All WAIS-V data were calculated and illustrated. One outlier was plotted as one individual larger point

score and PTA could improve the linear model. Third, an analysis of "residuals" (partial correlation) was carried out to assess the direct association between GDT and PTA with confounding effects from age, gender and working memory. Fourth, principal component analysis (PCA) was performed to convert original pure tone threshold measurements into a few linearly uncorrelated variables (principal components) by orthogonal transformation. The linear relationship between GDT and principal components was examined. Finally, with PTAs as repeated measures, a linear mixed effect model was used to assess the pure tone threshold variation and to focus on possible associations between peripheral and central ARHI, considering individual participant's random effect and complex covariance structure.

3 | RESULTS

3.1 | Data description

Demographic and performance data for the two WUSTL participant groups are shown in Table 1. The data were analyzed for a total of 156 subjects. Thirty-six were older adults with good hearing (GE; mean age = 66), 76 were older adults with hearing loss (No_GE; mean age = 73), and 44 were young adults (mean age = 21). Among the GE, No-GE, and Young groups, there were more female (n = 109) than male participants (n = 47). For the GDT data, the mean for all subjects was 12.52 ms. Data for possible correlations between GDT and age from all subjects are presented (Figure 1a), and a weak correlation

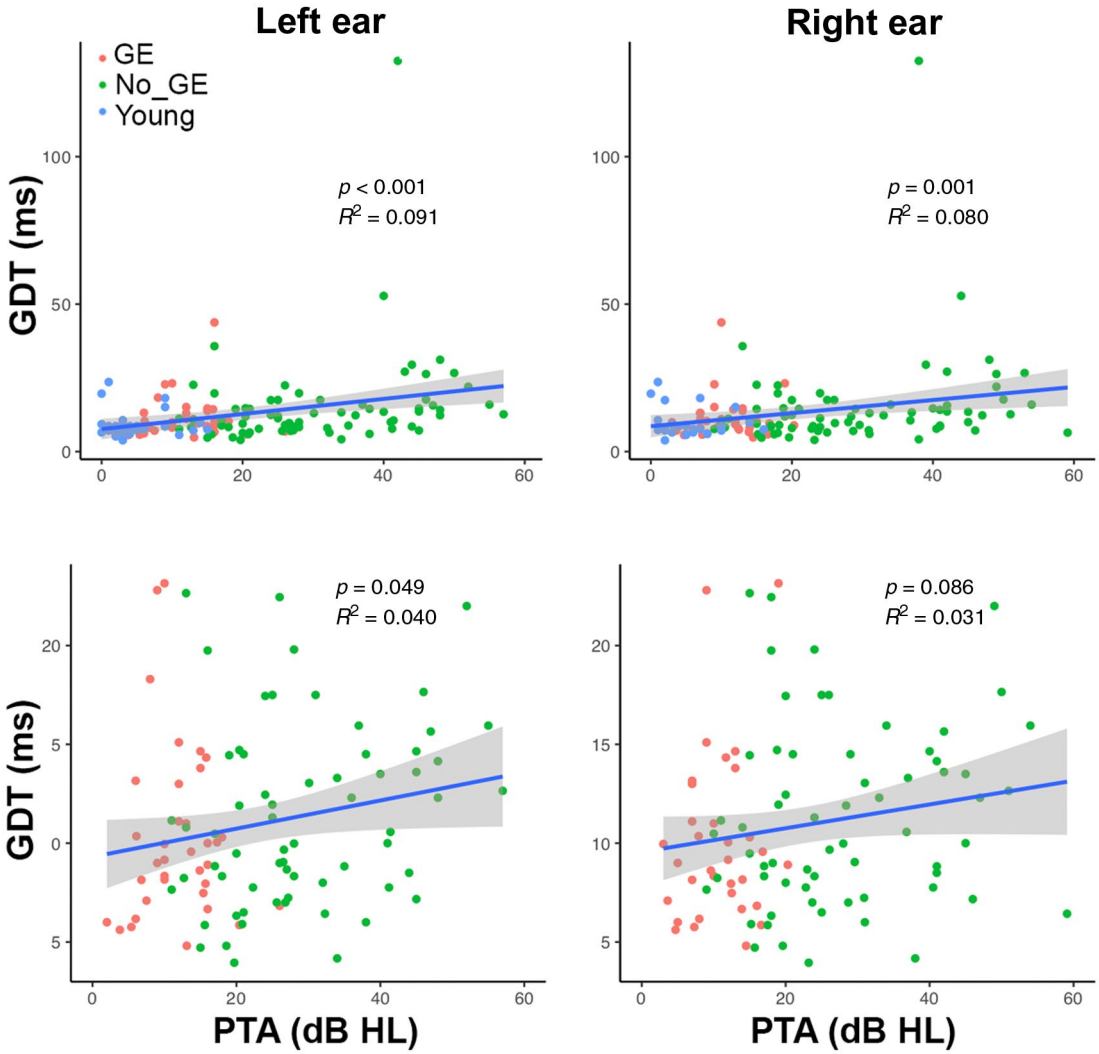

FIGURE 3 Data distribution for GDTs and PTAs. (a) All GDT and PTA data from left ears were calculated and illustrated for the three groups. (b) All GDT and PTA data from right ears were calculated and illustrated for the three groups. (c) GDT and PTA data from left ears without the young adults and nine outliers from older adults were calculated and illustrated. (d) GDT and PTA data from right ears without the young adults and nine outliers from older adults were calculated and illustrated. The scale level for the bottom two panels is much smaller than the level of the top two panels. No significant association between GDT and PTA was observed within older adults without outliers

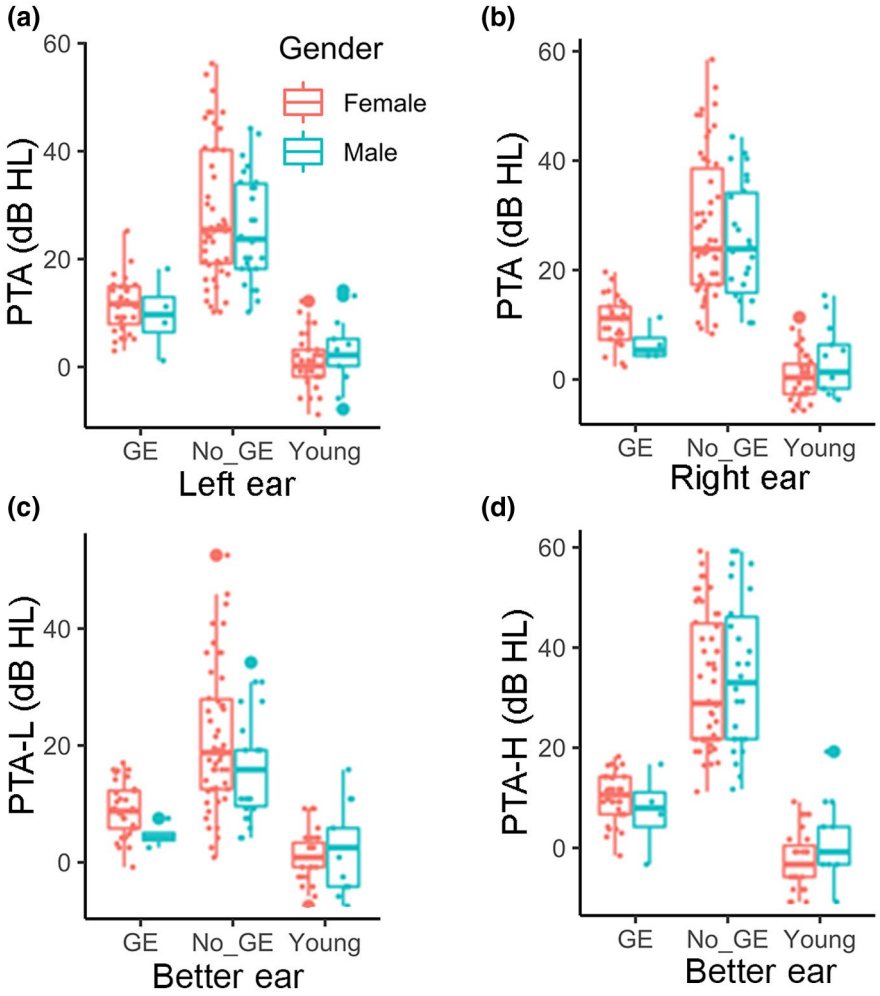

FIGURE 4 Data distribution for PTAs among young and older adult groups. (a) PTA of all five frequencies for the left ear were calculated and illustrated. (b) PTA of all five frequencies for the right ear were calculated and illustrated. (c) PTA-L (an average of hearing thresholds at 0.25, 0.5, and 1 kHz) for the better ear were calculated and illustrated. (d) PTA-H (an average of hearing thresholds at 2 and 4 kHz) for the better ear were calculated and illustrated. Outliers (outside the first and third quartiles) were plotted as larger points

between GDT and age was observed (p = 0.029, R^2 = 0.032). This correlation became stronger after outliers were removed from the data set (Figure 1b; p = 0.005, R^2 = 0.056). The outliers were identified based on the standard definition which is less than the first quantile (Q1) or greater than the third quantile (Q3) by more than 1.5 times the interquartile range (IQR = Q3–Q1). Nine outliers from the WUSTL data were identified in this way. The boxplot without these nine outliers (Figure 2a) shows a few new outliers, indicating highly variable GDTs. In contrast, few outliers were found for WAIS-V scores (Figure 2b). In addition, no gender differences were observed for either GDTs or WAIS-V scores, however, this could be due to the small male sample size. Data for correlations between GDT and PTA from all subjects are presented for both left (Figure 3a,c) and right ears (Figure 3b,d), with a weak correlation observed for both ears (Figure 3,ab). However, this correlation became much weaker after data from young subjects and outliers were removed from the data set (Figure 3c,d). In addition, boxplots showed similar patterns for left (Figure 4a) and right (Figure 4b) ears, and for low-(Figure 4c) and high-(Figure 4d) frequency ranges. Hearing thresholds were poorer and more variable in older adults with hearing loss compared to those from young adults or older adults without hearing loss. Finally, we analyzed all continuous variables with a correlation matrix (Figure 5). Not surprisingly, age and hearing thresholds at each test frequency were correlated, and hearing thresholds were better correlated when test frequencies were nearer one another. No correlation was observed between GDT and hearing thresholds at each test frequency or GDT and WAIS-V score.

3.2 | Auditory temporal processing—Effects of age, gender, PTA, and WAIS-V scores

Consistent with previous studies (Humes et al., 2012), t-test results showed that GDTs of young adults were significantly different from older adults (p < 0.002); while there was no significant difference between the GE and No_GE groups within older adults

(p < 0.092). To further determine if any of the variance in GDTs could be attributed to age, gender, hearing ability (PTA-L or PTA-H) or cognitive function (WAIS-V), three stepwise linear regression models were used (Table 2). From Model 1, the age effect was significant (p < 0.001), but its effect size was not very large (coefficient = 0.065; R^2 = 0.123). The outcome of Model 2 indicated that the age variable was still a significant predictor of GDT after including gender and WAIS-V in the model. In Model 3 (the full model), now including PTAs, age was still a significant predictor, while PTA-L, PTA-H, gender, and WAIS-V were not significant. Finally, with a null hypothesis that the reduced model (the simplest one) was enough compared to the full model, we compared these three models with a likelihood ratio test. The simplest model (Model 1), which included only age as the predictor, was the best model, indicating again that age was the most important factor for GDTs. In order to control for the age effect, we repeated our analysis within older adults (Table 3). Again, we failed to find any influences from PTA-L, PTA-H, gender, or WAIS-V that could be a significant predictor of GDTs.

Next, we performed a "residuals" analysis (partial correlation) to focus on any direct correlations between peripheral hearing loss and temporal processing (Figure 6, Table 4). The partial correlations between PTA-L and GDT (R = 0.084, p = 0.39), and PTA-H and GDT (R = 0.071, p = 0.47) were both non-significant, indicating that after controlling for the confounding factors of age, gender and cognitive function, there was no evidence supporting an association between PTA and GDT. To examine possible effects of hearing loss and GDTs further, we applied PCA to reduce the dimension of 10 pure tone hearing threshold measurements, which resulted in PC1 being the weighted average of the 10 pure tone hearing threshold measurements and PC2, the hearing threshold contrast between low and high frequencies. Together, PC1, 2, and 3 could explain 63.77% of the variation among 10 pure tone hearing threshold measurements (Figure 7). Importantly, age was still the only significant predictor while gender, WAIS-V scores, and PC1, 2, and 3 accounted for very little of the variance in GDTs (Table 5). A likelihood ratio test using the reduced model (with age only) and the full model also suggested the simple model was better (p = 0.428). Thus, there was no evidence to suggest that PC1, PC2, or PC3 was associated with GDTs.

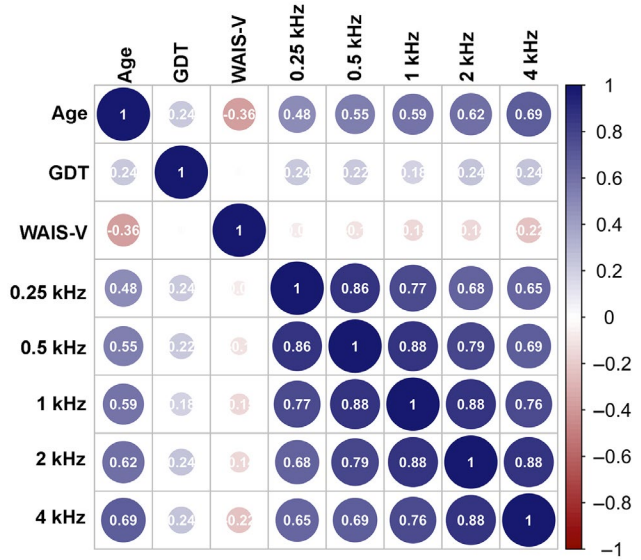

FIGURE 5 A correlation map for all continuous variables. The extent of correlation was illustrated by the color (left bar for the color representation) and the circle size, with one as the highest correlation and zero as no correlation. Each number was obtained using Pearson correlation between two variables

Because age-related changes in top-down controls (e.g., medial olivocochlear efferents; Fu et al., 2010) could influence hearing thresholds, and since pure tone hearing threshold measurements could be treated as repeated measurements, a linear mixed effect model with a compound symmetry covariance matrix was used to investigate possible associations of other factors with pure tone hearing thresholds (Table 6). This model used age, gender, GDT, WAIS-V, and test frequency to explain pure tone hearing thresholds. This analysis not only examines the linear relationship between pure tone hearing threshold and GDT, but also considered participants' individual random effects and correlations between repeated hearing measurements, which is more advanced and appropriate to use with our study design. The only significant factor was age (p < 0.001). The type 3 analysis of variance of fixed effects suggested that age (p < 0.001) and frequency (p < 0.001) were significant factors, while gender, GDT and WAIS-V were not significant. In short, with this mixed model, we continue to find no evidence in support of an association between GDT and PTA.

In summary, the statistical analyses of the WUSTL data suggested that peripheral hearing loss and central temporal processing were not associated. These analyses were conducted excluding data from nine outliers. Recent studies in the field of genetics suggest that examination of outliers (extreme phenotype analysis) could also reveal fundamental biological mechanisms (e.g., Bjørnland, Bye, Ryeng, Wisløff, & Langaas, 2018). We adopted this approach here and observed the first case of a dramatic disassociation between hearing thresholds and GDTs (Figure 8). That is, some older adults without hearing loss (i.e., hearing thresholds <20 dB; 0.25 to 4 kHz) showed large GDTs (e.g., ONH-36), while some older adults with severe hearing loss (thresholds > 50 dB) could detect very small gaps (e.g., OHI-35). Thus, our analysis of these outliers provided additional evidence for a lack of association between GDT and PTA.

3.3 | No evidence for an association between GDTs with peripheral hearing loss at higher frequencies

Because high-frequency hearing loss may affect temporal processing in the low-frequency region (Leigh-Paffenroth & Elangovan, 2011; but also see Moore, Glasberg, Stoev, Füllgrabe, & Hopkins, 2012), we addressed whether age-related hearing loss at higher test frequencies contributed to poorer GDTs in older adults by considering an additional cohort of older adults (NEOMED) in which audiometric

TABLE 2 Three linear regression models of all WUSTL data

Model 1 (GDT = $\beta_0 + \beta_1$age + ε)				
	Estimate	***SE***	***t* value**	**Pr(>|*t*|)**
(Intercept)	7.686	1.014	7.582	0.000
Age	0.065	0.017	3.794	0.000
Observations	Residual *SE*		R^2	Adjusted R^2
105	4.492		0.123	0.114
Model 2 (GDT = $\beta_0 + \beta_1$age + $\beta_2$gender + β_3WAIS-V + ε)				
	Estimate	***SE***	***t* value**	**Pr(>|*t*|)**
(Intercept)	3.57	3.373	1.058	0.292
Age	0.074	0.019	3.994	0.001
GenderMale	−0.118	0.952	−0.124	0.902
WAIS.V	0.072	0.056	1.284	0.202
Observations	Residual *SE*		R^2	Adjusted R^2
105	4.492		0.123	0.114
Model 3 (GDT = $\beta_0 + \beta_1$age + $\beta_2$gender + β_3WAIS-V + β_4PTA-L + β_5PTA-H + ε)				
	Estimate	***SE***	***t* value**	**Pr(>|*t*|)**
(Intercept)	4.254	3.502	1.215	0.227
Age	0.061	0.027	2.294	0.024
GenderMale	−0.112	1.053	−0.106	0.916
WAIS.V	0.063	0.057	1.102	0.273
PTA-L	0.030	0.064	0.469	0.640
PTA-H	0.006	0.048	0.118	0.907
Observations	Residual *SE*		R^2	Adjusted R^2
105	4.529		0.1429	0.100
Likelihood ratio test				
Reduced	**Full**	***p* value**		
Model 1	Model 2	0.442		
Model 2	Model 3	0.700		

thresholds through 16 kHz were measured. Demographic and performance data for the NEOMED cohort are shown in Table 7. For two older adults with hearing loss, hearing thresholds could not be obtained at high frequencies (Figure 9). Data for possible correlations between GDT and PTA for both GE and No-GE NEOMED subjects were presented for left (Figure 9a) and right ears (Figure 9b), and no significant correlations between PTA and GDT was observed for either ear based on overall PTAs. Furthermore, no significant correlations were observed either between PTA-UH (6, 8, and 10 kHz) and GDT (Figure 9c) or PTA-UH2 (12.5, 14, and 16 kHz) and GDT (Figure 9d).

Like the WUSTL study, PCA was applied to examine possible correlations between hearing loss and GDTs, reducing the dimension of 26 individual pure tone hearing threshold measurements of PTA measurements to 12 PCs. Again, although PC1 to PC6 could explain 81% variation of pure tone hearing threshold measurements (Figure 10), they accounted for very little of the variance in GDTs (Table 8). Next, we followed with additional statistical analyses. In unadjusted analyses, no significant associations were

TABLE 3 Linear regression Analysis of WUSTL data from older adults

	Estimate	***SE***	***t* value**	**Pr(>|*t*|)**
(Intercept)	12.5	0.711	17.59	0.000
Gender × Male	−0.163	1.25	−0.131	0.897
Fitting linear model: GDT~WAIS.V				
(Intercept)	8.991	3.150	2.854	0.006
WAIS.V	0.071	0.063	1.116	0.269
Fitting linear model: GDT~PTA				
(Intercept)	11.57	1.118	10.35	0.000
PTA	0.039	0.042	0.916	0.363
Fitting linear model: GDT~Low				
(Intercept)	11.66	0.987	11.82	0.000
PTA-L	0.044	0.045	0.981	0.331
Fitting linear model: GDT~High				
(Intercept)	11.74	1.15	10.22	0.000
PTA-H	0.024	0.034	0.709	0.481

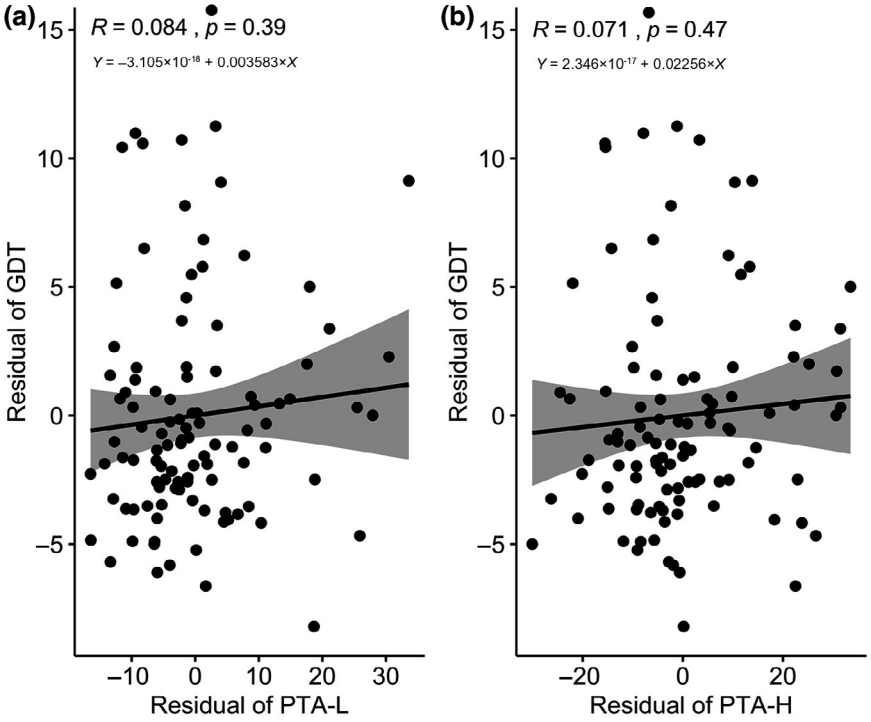

FIGURE 6 The partial correlation between hearing loss and GDTs. (a) The residual analysis of GDT and PTA-L (residuals Pearson correlation 0.084). (b) The residual analysis of GDT and PTA-H (residuals Pearson correlation 0.071)

TABLE 4 Partial correlation between GDT, PTA-L, and PTA-H

	GDT	PTA-L	PTA-H
GDT	1	0.084	0.071
PTA-L	0.084	1	0.747
PTA-H	0.071	0.747	1

observed between GDTs and the other independent variables of age, PTA-L, PTA-H, PTA-UH, and PTA-UH2 within the NEOMED cohort. When analyzed by individual test frequency, no significant association was observed for any of the 13 test frequencies. Gender was excluded from the analyses due to having only four male subjects. Next, the same linear mixed effect model was used (Table 9). This analysis showed, similar to the outcome from the WUSTL data, that there was no significant association between PTA and GDT, while age and frequency were still significantly correlated with PTA. Multiple regression analysis including all five variables yielded a very low correlation (r^2 = 0.009). Thus, the regression results suggest that PTA-L, PTA-H, PTA-UH, and PTA-UH2 have little or no relationship to GDTs. In addition, by applying an extreme phenotype analysis, we observed similar dissociations between hearing thresholds and GDTs (Figure 11). Three older adults with hearing loss at only high frequencies (NH-38) or at both low and high frequencies (HI-36 and HI-54) showed similarly small GDTs, consistent with a lack of association between GDT and PTA.

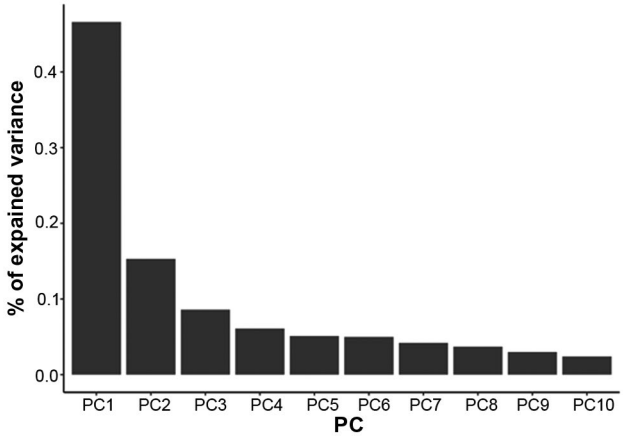

FIGURE 7 Principal component analysis (PCA) for hearing loss and GDTs. PCA reduced the dimension of pure tone hearing threshold measurements into 10 components. PC1, 2, and 3 could explain 63.77% of the variation among 10 pure tone hearing threshold measurements

4 | DISCUSSION

In order to determine if central ARHI could exist independently of peripheral ARHI, this study examined the relationship between gap detection and peripheral hearing. Statistical analyses suggested an association between GDTs and age, but not between GDTs and PTAs, gender, or WAIS-V scores. Furthermore, based on examination of outliers (or extreme phenotypes) between hearing and gap thresholds, we find no evidence to support that age-related declines

TABLE 5 Regression GDT on PC1, PC2, and PC3

Model: GDT = $\beta_0 + \beta_1$age + $\beta_2$gender + β_3WAIS-V + $\beta_4 PC_1 + \beta_5 PC_2 + \beta_6 PC_3 + \varepsilon$				
	Estimate	***SE***	***t* value**	**Pr(>|*t*|)**
(Intercept)	4.396	3.55	1.238	0.219
Age	0.057	0.028	2.049	0.043
GenderMale	0.143	1.064	0.134	0.894
WAIS-V	0.051	0.058	0.872	0.385
PC1	−0.012	0.013	−0.913	0.364
PC2	0.024	0.032	0.753	0.453
PC3	−0.077	0.048	−1.596	0.114
Observations	Residual *SE*	R^2	Adjusted R^2	
103	4.492	0.164	0.111	

TABLE 6 Tests of fixed effects

Effect	Num DF	Den DF	*F* value	Pr(>|*t*|)
GDT	1	99	0.67	0.4137
WAIS-V	1	99	3.08	0.0823
Gender (male–female)	1	99	0.75	0.3882
Age (old–young)	1	99	61.29	<0.0001
Frequency level	4	404	29.64	<0.0001
Gender*Age	1	99	0.58	0.4491
Gender*Frequency	4	404	9.61	<0.0001
Age*Frequency	4	404	40.99	<0.0001
Gender*Age*Frequency	4	404	3.03	0.0176

in central temporal processing are associated with age-related changes in peripheral hearing function. Thus, our data suggest that age-related changes of central temporal processing are not dependent on peripheral hearing function or age-related changes in working memory.

The strength of this study is that we have addressed three critical issues important to determine if peripheral and central ARHI can be uncoupled. First, because peripheral ARHI commonly starts at higher frequencies, most previous studies focused only on temporal processing abilities for sounds in low-frequency hearing regions. However, recent studies have demonstrated that GDTs tested in lower frequencies having normal hearing thresholds can be influenced by hearing loss at higher frequencies (e.g., Leigh-Paffenroth & Elangovan, 2011). Our study with the NEOMED cohort is the first one to consider possible correlations between GDTs and hearing thresholds up to 16 kHz. Second, because cognitive function can influence the outcome of auditory temporal testing, we utilized the verbal subset of WAIS-IV to assess working memory and employed a simple gap detection test to minimize possible cognitive interference (Harris et al., 2010). Third, within the older adult group, we applied statistical tools to study possible contributions of PTAs to GDTs or GDTs to PTAs and failed to detect associations between GDTs and PTAs. We also studied outliers with a method similar to genetic extreme phenotype analysis, and found that there were older participants with significantly elevated GDTs despite having peripheral hearing within normal range, and conversely, those with significant peripheral hearing loss having GDTs that were similar to those obtained from young normal hearing adults. Thus, these analyses provide several lines of evidence refuting the possibility that peripheral hearing loss mediates age-related declines in central temporal processing as reflected by GDTs. Overall, this lack of relationship between gap detection, peripheral hearing thresholds, and cognitive factors suggests that at least certain aspects of age-related central auditory processing changes can occur independently of peripheral hearing and higher brain functions. Since age-related deficits in gap detection may be due, in part, to changes in the brainstem (Allen, Burkard, Ison, & Walton, 2003; Barsz, Ison, Snell, & Walton, 2002; Poth, Boettcher, Mills, & Dubno, 2001; Walton, 2010), our results further support that age-related changes in the brainstem related to GDTs could be independent from peripheral hearing loss.

Although we did not detect an association between GDT and PTA, there are several factors to consider that may influence GDTs. First, consistent with previous studies (He, Horwitz, Dubno, & Mills, 1999; Humes et al., 2009, 2010, 2013; John, Hall, & Kreisman, 2012; Ozmeral et al., 2016; Snell & Frisina, 2000; Snell, Mapes, Hickman, & Frisina, 2002), GDTs were generally poorer in older participants compared to younger subjects under identical test conditions, where age-related deficits in selective attention could be a factor (Harris et al., 2010). Previous studies suggested that older adults compensated for attentional deficits by relying more on sensory processing (Harris, Wilson, Eckert, & Dubno, 2012; Leung, Jolicoeur, & Alain, 2015). Thus, age-related attention deficits could still contribute to age-related changes of GDTs if more complicated gap testing were used. Second, age-related declines in temporal processing may arise from age-related declines in both peripheral and central neural synchrony

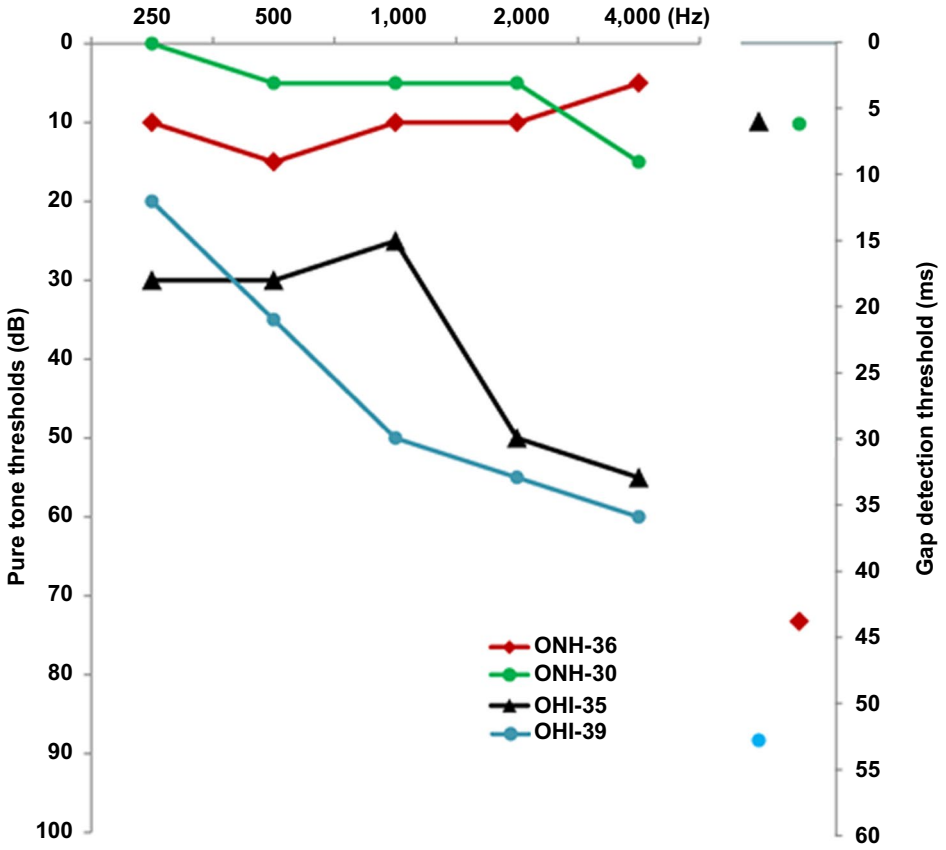

FIGURE 8 Lack of association between GDTs and peripheral hearing loss for outliers. Four individual cases are illustrated here with two cases having normal audiograms (ONH-36 and ONH-30) and two cases with peripheral hearing loss (OHI-35 and OHI-39). The audiogram data are shown on the left panel, and the right panel shows the single highest GDT measurement from each individual

TABLE 7 NEOMED participant characteristics and test performance

Older	
Number	14
Age range	57–79
Average age	63.42 ± 3.3
Gender (F/M)	10 F, 4 M
PTA-L (dB HL)	8.99 ± 8.1
PTA-H (dB HL)	17.07 ± 12/1
PTA-UH (dB HL)	36.81 ± 14.5
PTA-UH2 (dB HL)	65.31 ± 9.4
GDT (ms)	10.36 ± 1.7

Abbreviations: PTA-UH, pure one average of higher frequency (6 through 10 kHz); PTA-UH2, pure tone average of even higher frequency (12 through 16 kHz); ± followed by Standard deviation.

(Harkrider, Plyler, & Hedrick, 2005; Harris & Dubno, 2017; Harris, Mills, He, & Dubno, 2008; Tremblay, Billings, & Rohila, 2004). However, among older adults, different GDT scores are not associated with peripheral hearing loss. Thus, our data still imply an intrinsic aging process of the central auditory system. Third, GDTs were previously found to be longer in females than males (Ozmeral et al., 2016), and our study did not find a significant difference between male and female subjects. This could, however, be due to a lower proportion of male participants in our study. Fourth, in previous studies, age-related changes in both gap detection and speech perception have been documented, but significant correlations between these measures have been difficult to demonstrate (Schoof & Rosen, 2014; Strouse, Ashmead, Ohde, & Grantham, 1998). This variability in findings has been attributed in part to differences in methodologies employed across studies. Significant associations between gap detection thresholds and speech in noise perception have been demonstrated when speech is presented in a temporally complex background noise (e.g., speech babble or amplitude-modulated noise; Snell et al., 2002). Use of such speech tests would benefit future studies of central ARHI. Fifth, hearing loss has been shown to negatively impact the testing outcome of a backward digit span test, a measurement of working memory (Iliadou, Moschopoulos, Sidiras, Eleftheriadou, & Nimatoudis, 2018). Thus, it would be interesting to explore

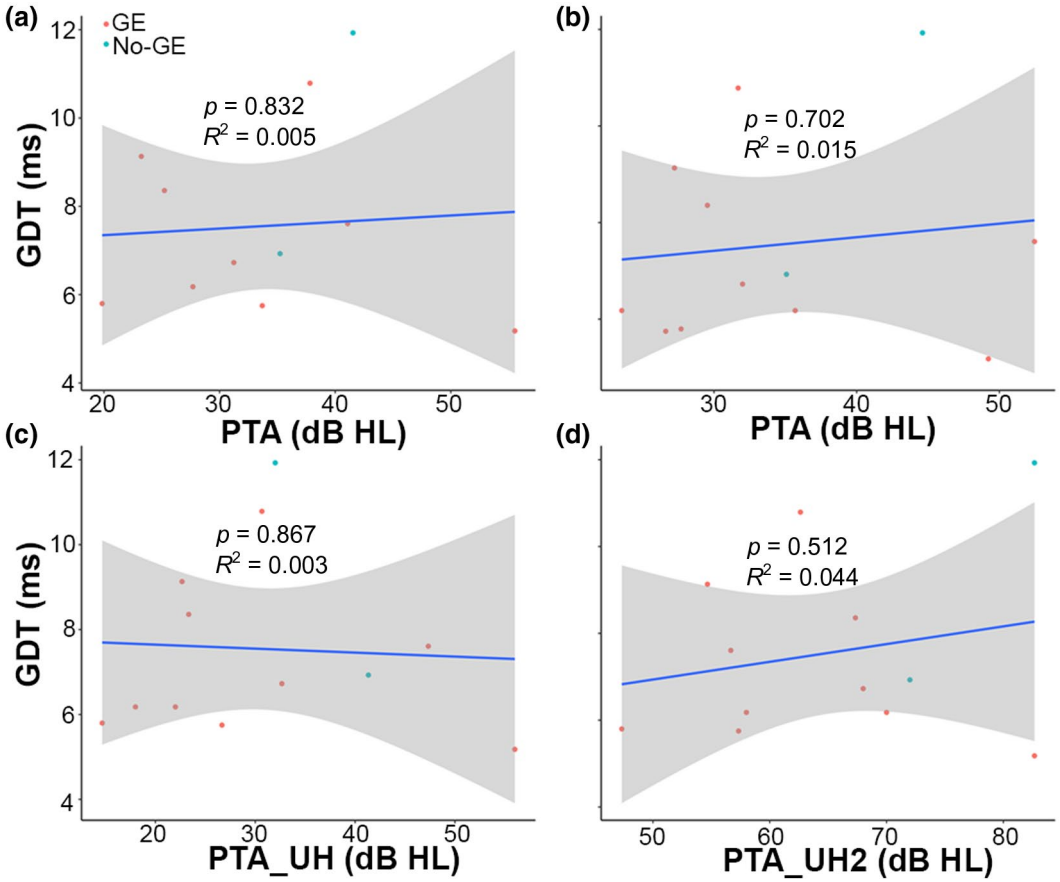

FIGURE 9 NEOMED data distribution for GDTs and PTAs for both ears. (a) All GDT and PTA data from left ears were calculated and illustrated. (b) All GDT and PTA data from right ears were calculated and illustrated. (c) GDT and PTA-UH data from the better ears were calculated and illustrated. (d) GDT and PTA-UH2 data from the better ear were calculated and illustrated. No significant association between GDTs and PTAs was observed

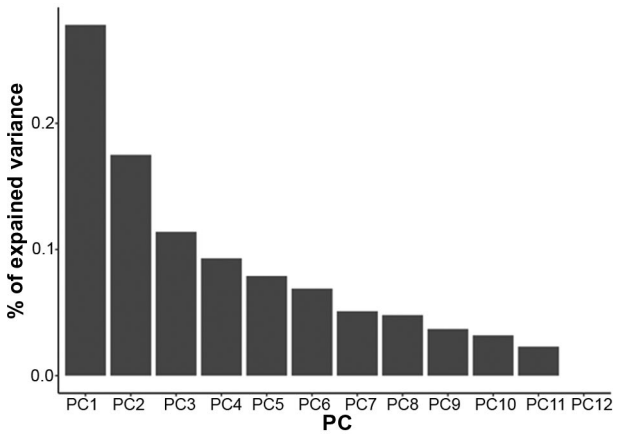

FIGURE 10 PCA for hearing loss and GDTs. PCA reduced the dimension of pure tone hearing threshold measurements into 12 components. The first six PCs could explain 81% variation among 26 pure tone hearing threshold measurements

TABLE 8 Regression GDT on PC1, PC2, and PC3

Model: GDT = $\beta_0 + \beta_1$age + $\beta_2 PC_1 + \beta_3 PC_2 + \beta_4 PC_3 + \varepsilon$)				
	Estimate	***SE***	***t* value**	**Pr(>|*t*|)**
(Intercept)	1.271	15.75	0.081	0.938
Age	0.103	0.258	0.399	0.702
PC1	0.046	0.215	0.216	0.836
PC2	0.092	0.341	0.269	0.796
PC3	−0.010	0.555	0.054	0.959
Observations	Residual Std. Error		R^2	Adjusted R^2
12	2.595		0.048	−0.495

whether a decline in temporal processing skills, such as GDTs, could also compromise the outcome of cognitive tests. Finally, we examined the possible link between temporal processing and hidden hearing loss and found no correlation between GDTs and hearing loss at higher frequencies (>8 kHz). This finding suggests that a synaptic loss between inner hair cells and SGNs with high thresholds (small afferent fibers) during aging may not contribute to age-related changes in GDTs. This provides a basis for future studies to further explore this relationship with more direct measurements, such as the Wave I amplitude of electrocochleographic recording.

TABLE 9 Possible correlations between GDT and PTA for NEOMED data

Coefficients	Value	*SE*	*t* value	*p* value
(Intercept)	14.487	65.699	0.221	0.827
Age	−0.093	1.081	−0.086	0.932
PTA_L	−32.949	34.217	−0.963	0.342
PTA_UH	−44.137	41.545	−1.062	0.295
PTA_UH2	43.913	74.493	0.589	0.559
GDT	0.492	1.096	0.449	0.656
Age:PTA_L	0.452	0.559	0.808	0.424
Age:PTA_UH	1.019	0.679	1.500	0.142
Age:PTA_UH2	0.140	1.218	0.115	0.909

Correlation	Age	PTA_L	PTA_UH	PTA_UH2	GDT
Age	−0.991				
PTA_L	−0.725	0.720			
PTA_UH	−0.174	0.173	0.376		
PTA_UH2	−0.587	0.583	0.656	0.570	
GDT	−0.010	−0.116	0.000	0.000	0.000

Standardized residuals:				
Min	Q1	Med	Q3	Max
−1.448	−0.577	−0.344	0.498	2.078

Note: Residual standard error: 8.481. Degrees of freedom: 48 total; 39 residual.

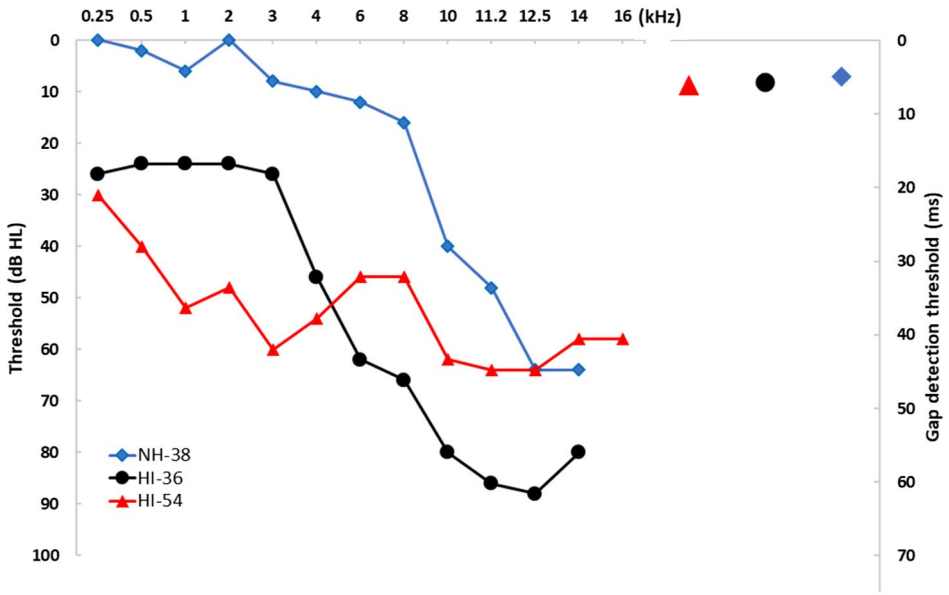

FIGURE 11 Lack of association between GDTs and peripheral hearing loss at higher frequencies. Three individual cases are illustrated here, one with normal (<20 dB HL; 0.25 to 8 kHz) audiometric thresholds (NH-38) and two with peripheral hearing loss (HI-36, HI-54). The audiogram data are shown in the left panel, and the right panel shows the single highest GDT measurement from each individual

5 | CONCLUSION

Overall, no significant associations were found between age-related declines in central temporal processing as measured by gap detection thresholds and age-related declines in peripheral hearing or cognitive function, which may be due to multiple independent processes. These findings imply that the current diagnostic and rehabilitative strategies for patients with presbycusis may not be enough for patients with both age-related hearing loss and temporal processing deficits.

DECLARATION OF TRANSPARENCY

The authors, reviewers, and editors affirm that in accordance with the policies set by the *Journal of Neuroscience Research* this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Conceptualization, J.B.; *Methodology*, J.B. and N.T.M.; *Investigation*, J.B., Y.Y., H.L., J.H., G.S., B.D., T.B., and B.S.; *Resources*, J.B.; *Writing – Original Draft*, J.B., J.H., H.W., T.B., B.S., and N.T.M.; *Writing – Review & Editing*, J.B., J.H., H.W., T.B., B.S., and N.T.M.; *Validation*, G.S.; *Visualization*, J.B., G.S., H.W., and B.S.; *Supervision*, J.B., J.H., and N.T.M.; *Project Administration*, J.B. and N.T.M.; *Funding Acquisition*, J.B. and N.T.M.; *Formal Analysis*, H.W., P.L., and B.S.; *Date Curation*, H.W., P.L., and B.S.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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