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# Behavioral characterization of the cochlear amplifier lesion due to loss of function of stereocilin (STRC) in human subjects

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## Abstract

Loss of function of stereocilin (STRC) is the second most common cause of inherited hearing loss. The loss of the stereocilin protein, encoded by the STRC gene, induces the loss of connection between outer hair cells and tectorial membrane. This only affects the outer hair cells (OHCs) function, involving deficits of active cochlear frequency selectivity and amplifier functions despite preservation of normal inner hair cells. Better understanding of cochlear features associated with mutation of *STRC* will improve our knowledge of normal cochlear function, the pathophysiology of hearing impairment, and potentially enhance hearing aid and cochlear implant signal processing. Nine subjects with homozygous or compound heterozygous loss of function mutations in *STRC* were included, age 7–24 years. Temporal and spectral modulation perception were measured, characterized by spectral and temporal modulation transfer functions. Speech-in-noise perception was studied with spondee identification in adaptive steady-state noise

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and AzBio sentences with 0 and −5dB SNR multitalker babble. Results were compared with normal hearing (NH) and cochlear implant (CI) listeners to place *STRC*$^{-/-}$ listeners' hearing capacity in context. Spectral ripple discrimination thresholds in the *STRC*$^{-/-}$ subjects were poorer than in NH listeners ($p < 0.0001$) but remained better than for CI listeners ($p < 0.0001$). Frequency resolution appeared impaired in the *STRC*$^{-/-}$ group compared to NH listeners but did not reach statistical significance ($p = 0.06$). Compared to NH listeners, amplitude modulation detection thresholds in the *STRC*$^{-/-}$ group did not reach significance ($p = 0.06$) but were better than in CI subjects ($p < 0.0001$). Temporal resolution in *STRC*$^{-/-}$ subjects was similar to NH ($p=0.98$) but better than in CI listeners ($p=0.04$). The spondee reception threshold in the *STRC*$^{-/-}$ group was worse than NH listeners ($p=0.0008$) but better than CI listeners ($p=0.0001$). For AzBio sentences, performance at 0 dB SNR was similar between the *STRC*$^{-/-}$ group and the NH group, 88% and 97% respectively. For −5 dB SNR, the *STRC*$^{-/-}$ performance was significantly poorer than NH, 40% and 85% respectively, yet much better than with CI who performed at 54% at +5dB SNR in children and 53% at +10dB SNR in adults. To our knowledge, this is the first study of the psychoacoustic performance of human subjects lacking cochlear amplification but with normal inner hair cell function. Our data demonstrate preservation of temporal resolution and a trend to impaired frequency resolution in this group without reaching statistical significance. Speech-in-noise perception compared to NH listeners was impaired as well. All measures were better than those in CI listeners. It remains to be seen if hearing aid modifications, customized for the spectral deficits in *STRC*$^{-/-}$ listeners can improve speech understanding in noise. Since cochlear implants are also limited by deficient spectral selectivity, *STRC*$^{-/-}$ hearing may provide an upper bound on what could be obtained with better temporal coding in electrical stimulation.

**Keywords**

Psychoacoustic; Auditory Threshold; Speech Perception; Genetic; Human; Cochlear amplifier

## 1. Introduction

Deafness is the most common congenital sensory deficit, affecting about 1/500 births worldwide (1–3). Roughly half of cases are genetic in origin and half of these are autosomal recessive. *GJB2* is the most commonly implicated gene in autosomal recessive hearing loss (about 50%) followed by *STRC* (about 10%) (1,3–6). However, *STRC*$^{-/-}$ deafness, also known as DFNB16, is likely underdiagnosed by genetic testing due to *STRC*'s regional genomic complexity and its close sequence similarity to the pseudogene *STRCP1*(7,8). *STRC* is located on chromosome 15q15.3 and named similarly to the protein it encodes, stereocilin. Loss-offunction mutations in STRC abolish expression of stereocilin protein in outer hair cells (OHCs). When present, this protein is located at the top of the OHCs stereocilia and connect the stereocilia to the tectorial membrane and the stereocilia between themselves. The only known consequence of absence of stereocilin is loss of the connection between these cells and the tectorial membrane leading to a disorganization of the OHCs stereocilia (9). Loss-of-function STRC mutations should therefore lead to a loss of active cochlear frequency resolution and amplifier function despite preservation of normal inner hair cells (IHC) as the stereocilin protein is not located in the IHC (10).

It is well-known that hearing loss causes impaired perception of speech-in-noise. Nevertheless, it is still unclear why patients have extremely variable speech perception, especially in noise, for the same hearing loss level. This variability also exists in Normal Hearing (NH) listeners (11–13). A better knowledge of underlying auditory mechanisms, particularly cochlear mechanisms associated with active frequency selectivity and amplification, could improve our understanding of these variable outcomes on speech perception tasks. Psychoacoustic testing can help to quantify the consequences of cochlear amplifier dysfunction. Such measures are correlated to the ability to discriminate cues in complex sounds such as spoken language, consonant or vowel identification (14–21).

The main objective of this study was to behaviorally characterize auditory mechanisms in individuals presenting with a bi-allelic loss-of-function of *STRC (STRC*$^{-/-}$*).* These findings may lead to a better understanding of the cochlear amplifier and can possibly be used to improve hearing aid algorithms for this population. In addition, greater understanding of the effects of loss of active cochlear filtering may allow for enhancement of cochlear implant signal processing.

We hypothesized that the loss of OHC function leads to the loss of frequency selectivity, and should impair the frequency resolution in STRC$^{-/-}$ subjects compared to NH listeners. Frequency resolution should still be better than in cochlear implanted (CI) subjects given the normal population of inner hair cells. The temporal resolution should not be impaired by the loss of function of the outer hair cells, as the IHCs function remains normal. We expect reduced speech in-noise perception in STRC$^{-/-}$ subjects relative to NH due to the impaired frequency resolution.

## 2. Material and Methods

This work has been carried out in accordance with the Declaration of Helsinki and Institutional Review Board approval at the Seattle Children’s Hospital and the University of Washington were obtained prior to initiation of the study.

### 2.1. Subjects

Subjects were identified in a previous study at the University of Washington in which 449 subjects presenting with bilateral sensorineural hearing loss of onset under 18 years were sequenced with a custom hearing loss gene panel of 190 genes including *STRC* (6). For the present study, participants with homozygous or compound heterozygous loss of function mutations in *STRC* were selected. Loss-of-function mutations included complete gene deletions and point mutations leading to early truncation (nonsense or frameshift). Participants were required to be older than 7 years and able to complete all of the study tasks. Subjects with middle ear disease were excluded and all selected subjects had a similar audiogram with normal speech discrimination in quiet (Figure 1).

Thirty-two subjects who fit the above criteria were identified. Nine who lived near Seattle, who spoke English as a first language, and who did not have evidence of middle ear disease in their medical record were contacted and included in this study. They are grouped below as the “*STRC*$^{-/-}$ group”. Five of them were assigned female at birth (55.6%). The mean

age at inclusion was 12.5 years (+/− 5 years). All wore bilateral hearing aids. Hearing loss was diagnosed at a mean age of 4 years (+/− 2.4 years) and hearing aids were fitted at a mean age of 4.9 years (+/− 2.6 years). All demographic characteristics of this population are summarized in Table A. Demographic characteristics for NH listeners and listeners with cochlear implants were extracted from Horn *et al.* (2017) and Park *et al.* (2015) and are summarized in Table B (22,23).

Figure 1 and Table A report participants' pure tone average thresholds for each tested frequency for their first and last audiograms. Hearing loss was stable through frequency, subjects and time. Participant speech discrimination, tested in a routine clinical manner, was normal. Comparative data for NH listeners and listeners with CIs were extracted from Horn *et al.* (2017), Park *et al.* (2015), Drennan *et al.* (2007), Jung *et al.* (2012) and Holder *et al.* (2016) (22–26). Informed consent was obtained prior to all tests for all subjects. If subjects were minors, informed consent was obtained from their parent or legal guardian and an informed assent form adapted to the subject's age (7–13 years old or 14–17 years old) was signed by the minor. Subjects were compensated at an hourly rate consistent with other behavioral studies in the Virginia Merrill Bloedel Hearing Research Center.

## 2.2. Stimuli and procedures

All of the following tasks were performed in a double-walled, soundproof booth. Stimuli were presented in the free-field through a loudspeaker positioned at 0° azimuth, 0° elevation and at 1 m from the subject. The total duration of all tests was 3 to 4 hours including breaks. To minimize this potential attention deficit, the test sessions for children were planned in two half sessions if the parents agreed. All of the following procedures were run by the same examiner. All $STRC^{-/-}$ subjects were tested without hearing aids for all tasks.

The stimulus was presented via a loudspeaker to keep the protocol consistent with the comparative studies of Park *et al.* and Horn *et al.* (22,23). Fixed marks on the ground were placed before testing the first subject and until testing the last one to maintain an identical distance between the subject and the loudspeaker during the experiment for all participants, and the speaker calibration was systematically checked.

### 2.2.1 Spectral modulation perception

**2.2.1.1 Spectral Ripple density Discrimination (SRD) thresholds at fixed ripple depth:** This task utilized the same procedure as the one described in Horn *et al* (22,26).

Stimuli were constructed from summing 2555 pure-tone frequency components (bandwidth 100–5000 Hz) with a duration of 500 ms including rise/fall ramps of 15 ms. The component amplitudes followed a full-wave rectified sinusoidal envelope on a logarithmic amplitude scale with peaks spaced equally on a logarithmic frequency scale. Standard (reference) stimuli were created with random spectral envelope starting phases from 0 to $2\pi$. For each standard stimulus, a corresponding stimulus was created with a starting phase shifted by $\pi/2$. Ripple densities of the stimuli varied by ratios of 1.414 from 0.125 to 11.317 ripples per octave (RPO). Stimuli were presented at 61dBA in the sound field. On each trial, 3 stimuli, respectively corresponding to three boxes labelled "1", "2" and "3" on an LCD screen,

were presented with 200 ms interstimulus intervals. Two of the stimuli were standard and one of the three stimuli was a shifted stimulus (phase-shifted by π/2 radians). The subjects were asked to select the box corresponding to the stimuli that sounded different. They were asked to focus on the pitch and not on the loudness. No feedback was given. Ripple density was then varied adaptively in a 2-down (higher RPO) and 1-up (lower RPO) procedure to determine SRD thresholds converging on 70.7% correct. Threshold for one adaptative track was estimated by averaging the final 8 of 13 reversals (28). Minimum step sizes were in ratios of 1.414 ripples per octave. Four ripple depths were tested 5, 10, 13 and 20 dB, in a randomized order, and were maintained constant for each adaptative track. Two runs were repeated to determine threshold for each modulation depth. Thresholds of both runs were averaged.

**2.2.1.2. Spectral Modulation Transfer Function (SMTF):** To study specifically the frequency resolution and sensitivity to intensity modulation, both related to the performance on SRD, we fitted the SMTF with the SRD thresholds (23). This function is ruled by the following SMTF equation, $f(x) = b*ln(x/A)$ in Horn *et al.* (2017) (23). In this fitting function, $f(x)$ is the modulation density threshold and $x$ is the modulation depth. The coefficient $b$ describes the slope of the SMTF and so, its shape. It estimates the frequency resolution which is better when $b$ increases. The coefficient $A$ describes the sensitivity to spectral modulation which is worse when $A$ increases. While $A$ is affected by auditory and non-auditory-specific factors, such as intensity resolution, internal noise, listener inattention, coefficient $b$ should reflect frequency resolution independently from these other factors.

To be able to perform statistical analysis and compare the frequency resolution and the sensitivity to modulation between each group, we fitted an individual SMTF function for each subject but also an average SMTF fitting function for the average SRD thresholds at each modulation depth tested. To fit this function, we used a Microsoft Excel ® program using nonlinear least-squares regression to adjust the function to individual or average SRD thresholds to obtain the corresponding coefficients $b$ and $A$. The program rejected the function if the $R^2$ value was below 0.5. None were rejected in this study.

**2.2.1.3 Spectral Ripple Discrimination thresholds at fixed ripple density:** This task utilized the same procedure as the one described in 2.2.1.1 but instead of a fixed modulation depth, the ripple density was fixed to determine the modulation depth threshold. Modulation depth was varied adaptively in a 2-down (smaller depth, more difficult) and 1-up (larger depth, easier) procedure to determine modulation depth thresholds converging on 70.7% correct by averaging the modulation depth for the final 8 of 13 reversals for each adaptative track (28,29). The modulation depth step size was 2 dB until the third reversal and then 1 dB for the last 10 reversals. The spectral ripple discrimination thresholds at fixed modulation density have been determined here for spectral densities of 0.5 and 1 RPO in a randomized order, with 2 adaptative tracks for each. Thresholds of both tracks were averaged. These thresholds were not used to calculate the SMTF.

### 2.2.2. Temporal modulation perception

**2.2.2.1. Temporal Modulation Detection Thresholds (TMD thresholds):** The TMD thresholds task utilized the same procedure as the one described in Park *et al* (22,30). Subjects were presented with 2 s acoustic stimuli made up of a 1 s sinusoidally amplitude modulated wide band noise, and a 1 s of unmodulated wide band noise. Both the modulated and unmodulated signals were gated on and off with 10 ms linear ramps, then concatenated with no gap between the two signals. The first half of the acoustic stimuli corresponded to a box labelled “1” on the LCD screen and the second half to a box labelled “2”. A two-interval, two-alternative adaptive forced choice procedure was used to determine the TMD thresholds for the six modulation frequencies 10, 50, 100, 150, 200, and 300 Hz. Stimuli were presented at 65 dBA. Subjects were instructed to select the box corresponding to the modulated noise (first or second half of the acoustic stimuli). Visual feedback was provided after each sound presentation. A two-down, one-up adaptive procedure was used to measure the modulation depth threshold, converging to 70.7% (28). The tracking history started with a modulation depth of 100% (corresponding to 0dB modulation depth) and decreasing in steps of 4 dB until the fourth reversal, and 2 dB for the next 10 reversals. The TMD thresholds for one adaptative track was estimated by averaging the final 10 of 14 reversals. The different modulation frequencies were tested in a randomized order. Two adaptive tracks were repeated to determine the average thresholds. Thresholds of both runs of each modulation frequency were averaged. If the difference between the thresholds of the first two runs exceeded 3dB, an additional third run was performed.

**2.2.2.2. Temporal Modulation Transfer Function (TMTF):** To isolate the temporal resolution and sensitivity to temporal modulation, we fitted the TMTF with the mean TMD thresholds. This function is ruled by the following TMTF equation $f(x) = Ae^{bx}$ in Won *et al.* (31). In this fitting function, $f(x)$ is the value of the TMD for the modulation frequency $x$. The coefficient $b$ describes the slope of the function and so, its shape. The function shape estimates temporal resolution which is better when $b$ increases. The coefficient $A$ describes the TMTF height or the sensitivity to temporal modulation, which is better when $A$ increases. Like with SMTF, the TMTF $A$ coefficient is affected by both auditory and non-auditory factors while coefficient $b$ is independent from these factors.

To be able to perform statistical analysis and compare the frequency resolution and the sensitivity to modulation between each group, we fitted an individual TMTF function for each subject but also an average TMTF fitting function for the average TMD thresholds at each modulation rate tested. To fit this function, we used a Microsoft Excel ® program using nonlinear least-squares regression to adjust the function to individual or average TMD thresholds to obtain the corresponding coefficients $b$ and $A$. The program rejected the function if the $R^2$ value was below 0.5. None were rejected in this study.

### 2.2.3. Speech in-noise perception

**2.2.3.1. Spondee in steady-state noise:** The spondee in steady-state speech-shaped noise task utilized the same procedure as in previous studies at the Virginia Merrill Bloedel Hearing Research Center (22–24,27). A one-down one-up adaptive tracking procedure was used to determine thresholds which converged on 50% of correct answers (Speech Reception

Threshold-SRT) (28,32). Subjects sat in front of an LCD screen with twelve boxes, each labelled with a spondee word of equal difficulty (e.g., “birthday”, “padlock”, “sidewalk”, “northwest”, “toothbrush”, “mousetrap”, “stairway”, “iceberg”, “eardrum”, “woodwork”, “playground”, “drawbridge”). All spondee words used in this task were recorded by a female talker with a fundamental frequency ranging between 212 and 250 Hz. One spondee was presented randomly in the presence of steady-state noise (22,27,32). The level of the target speech was fixed at 65 dBA. Subjects were instructed to identify the word they heard by selecting the corresponding box on the screen. Duration of the steady-state speech-shaped noise was 2 s and the onset of the spondees was 500 ms after the onset of the noise. The noise level was varied with a step size of 2 dB. Feedback was not provided. For all subjects, the adaptive track started with +10 dB signal-to-noise ratio (SNR) condition. Due to the level of the target speech and the background noise level increasing as the task progressed, the background noise could become too loud and uncomfortable. If the subject complained of such discomfort, the task was restarted entirely with a level of the target speech at 60 dBA and with a starting SNR of +20 dB. The threshold for one adaptive track was estimated by averaging the signal-to-noise ratios for the final 10 of 14 reversals. Three adaptive tracks were repeated to determine the average thresholds.

The Spondee test was chosen to match procedures used by Drennan *et al.* and Jung *et al* (24,25). Before the beginning of the Spondee test, the examiner checked that each word was known to the subject. The background noise chosen for this task was steady-state because of previous studies showing that steady-state noise resulted in more consistent thresholds and limited variability between subjects as compared with multi-talker babble (24,33,34).

**2.2.3.2. AzBio sentences:** Twenty sentences, picked from one of the 16 pediatric AzBio test lists, were presented in the presence of a babble-noise (35). The pediatric AzBio test list was chosen randomly. After hearing the sentence, subjects were instructed to repeat each word they heard and guess the word if they were not sure. The same testing materials and procedure were used for both children and adults. The sentences were recorded by a female talker. The level of the target sentence was fixed at 65 dBA. First, the subject was trained to identify the female voice with 5 sentences from a training list played in quiet. The stimulus level was confirmed as comfortable but sufficiently loud for the subject. We increased the level of the target sentence to 70 dBA if the subject complained of difficulties understanding the female voice in quiet. For all subjects, the noise level started with −5 dB SNR condition. Feedback was not provided. The observer scored the number of words correctly repeated to obtain a sentence recognition performance (% of key words correctly repeated). This speech perception task was repeated a second time, at the same SNR, with another list of 20 sentences picked randomly from the pediatric AzBio test lists. The sentence recognition performances were then averaged. If the average score was below 50%, the test was fully run another time with 0 dB SNR. The pediatric AzBio was used to keep the material identical across our range of subject ages and allowed comparison with a variety of other studies of normal hearing and cochlear implanted subjects.

### 2.3. Statistics

All statistical analyses detailed below were conducted using SPSS Version 24 (IBM Corp., 2016) ®.

To determine if observed differences between hearing method groups were significant, a two-way repeated measures analyses-of-variance (ANOVA) were performed with thresholds (SRD or TMD thresholds) as the dependent variable and hearing group as the between-subjects variable. The within-subjects variable was modulation depth or rate for analyses of SRD and TMD threshold respectively. To analyze the differences in individual SMTF and TMTF coefficients *b* and A, between hearing-groups, two sets of one-way ANOVAs were conducted with these coefficients as dependent variables. To compare Spondee Reception Thresholds across hearing method groups, a one-way ANOVA was conducted. For all analyses, tests of variance homogeneity were conducted and the appropriate parametric vs. non-parametric statistics were used. Results with $p < 0.05$ were considered significant.

For the spectral task, we expected a significant main effect of hearing method group with performance in the $STRC^{-/-}$ group between NH and CI listeners. We also expected a significant interaction between hearing group and modulation depth reflecting a difference in the shape of the SMTF between groups. We also expected a main effect of hearing method group on coefficient *b* reflecting differences in frequency resolution across groups, with the $STRC^{-/-}$ group between NH and CI listeners. For the temporal task, we expected the $STRC^{-/-}$ group performance and TMTF coefficient *b* to be similar to the NH listeners. For Spondee Reception Threshold, we expected a significant main effect of hearing method group with performance in the $STRC^{-/-}$ group somewhere between NH and CI listeners.

## 3. Results

### 3.1. Spectral modulation perception

#### 3.1.1. Characteristics of SRD thresholds at fixed ripple depth in $STRC^{-/-}$ subjects (Figures 2.a, 2.b and Tables C and D)—

For ease of interpretation, we use the same axes for both functions with modulation depth on the y-axis. Therefore, we plotted the spectral task data (Figures 2a and 2b) with mean SRD threshold on the x-axis and the ripple depth tested on the y-axis. Figure 2.a shows the mean SRD thresholds for each conditions tested (solid lines with symbols) and the SMTF (dashed lines without symbols), after fitting the average SRD thresholds with the SMTF equation, for the $STRC^{-/-}$ group with comparison to prior data for NH and CI children. For all three groups, SRD thresholds increase with ripple depth. Because each group's SMTF is directly extracted for their respective mean SRD thresholds, both curves are very close on this graph. Figure 2b shows individual SRD thresholds for each condition tested. On both Figure 2a and 2b, the easiest conditions are towards the bottom of the y-axis and the best results are on the right of the x-axis. In other words, on these graphs, the curve representing the group with the best results is the one at the top right of the graph.

Statistical analysis was first performed on the SRD thresholds for each modulation depth tested. The statistical analysis of the effect of hearing method group and modulation depth on SRD thresholds revealed a significant main effect of group, with a significant difference

in SRD thresholds between *STRC*$^{-/-}$ and NH groups, between *STRC*$^{-/-}$ and CI groups, and between NH and CI groups ($p < 0.0001$), and modulation depth ($p < 0.0001$), with a significant interaction (F (degrees of freedom) = 14.821; $p < 0.0001$; $\eta 2$ (partial Eta squared) = 0.505).

Table C shows the different average coefficients *b* and *A*, underlying the SMTF fitted from the SRD thresholds, according to the 3 groups considered. The average coefficients *b* and *A* were obtained after fitting all individuals' data with the SMTF equation, to get for each subject, individual coefficients *b* and *A* that we averaged across subjects. Mean *b* coefficient of NH children is about 22% higher, meaning a better frequency resolution, than the *STRC*$^{-/-}$ group and more than 200% higher than the CI children. For the coefficient *A*, the coefficient of the NH children is 61% to 65% lower, meaning a better sensitivity to spectral modulation than for the *STRC*$^{-/-}$ and CI groups respectively. Statistical analysis revealed a significant effect of hearing group coefficient *b* ($p < 0.0001$; Table D). The effect of hearing group on coefficient *A* did not reach significance ($p = 0.241$).

The post-hoc analysis conducted on the SMTF *b* coefficient (Tukey) found a significant difference between the *STRC*$^{-/-}$ and the CI group ($p = 0.0155$) and between the NH and the CI groups ($p < 0.0001$) while the p-value, when comparing the *STRC*$^{-/-}$ and NH group, approaches significance without reaching it ($p = 0.0641$) (Table D). However, the significant interaction, found on the SRD thresholds analysis, between hearing group and modulation depth ($p < 0.0001$) suggests a difference in SMTF shapes between the different groups. This difference is consistent with impaired frequency resolution in the *STRC*$^{-/-}$ group compared to NH listeners.

We noticed that the NH group included one subject with outlying thresholds compared to other NH listeners (Figure 2.b). Thus, we also carried out our analysis on spectral processing by removing this outlier and found a significant difference between the average coefficient *b* of the STRC$^{-/-}$ group and NH group ($p = 0.013$), supporting an impaired spectral processing and frequency resolution in the STRC$^{-/-}$ group. We use the full data set in our analyses but present Figure 2.b to provide better clarity to our assertions.

#### 3.1.2. Characteristics of SRD thresholds at fixed spectral ripple density—

Ripple depth detection thresholds were estimated for 0.5 and 1 RPO of fixed ripple density. These thresholds had a high variance between subjects for each fixed ripple density tested. In our *STRC*$^{-/-}$ group, the mean ripple depth detection threshold at 0.5 RPO was of 8.1 dB (+/− 3.5 dB) and at 1 RPO was of 9.2 dB (+/− 3.9 dB). These results showed slight worsening thresholds with increased spectral density and also indicated higher (worse), thresholds in *STRC*$^{-/-}$ subjects than in the NH group reported in Anderson *et al.* (36), who reported thresholds in NH listeners ranging at 0.5 RPO from 5 to 12 dB and at 1 RPO from 4 to 5 dB. However, *STRC*$^{-/-}$ subjects' results were better than in CI listeners from Anderson *et al.*, where results varied from 5 to 27 dB at 0.5 RPO and from 6 to 31 dB at 1 RPO.

### 3.2. Temporal modulation perception (Figure 3 and Tables E and F)

Figure 3 shows the TMD thresholds for each condition tested (solid lines with symbols) for the *STRC*$^{-/-}$ group and for the NH and CI children as well as the TMTF (dashed

lines without symbols) for the three groups after fitting the average TMD thresholds with the TMTF equation. The coefficient *b* describes the function shape indicates the temporal resolution. The coefficient *A* describes the TMTF height on the y-intercept, and estimates the sensitivity to temporal modulation. The graph plots mean thresholds (y-axis) for the six modulation rates tested (x-axis). Because each group's TMTF is directly extracted for their respective mean TMD thresholds, for each group both curves are very close on this graph. On this graph the most difficult conditions are the right of the x-axis and the thresholds towards the top of the graph are the best thresholds. In other words, on this graph as well, the curve representing the group with the best results is the one located at the top right of the graph. For all three groups, temporal modulation detection thresholds increase, meaning that they are less negative or worse, as the modulation rate increases and so, as the task gets harder. However, they increase faster in the CI children, who have the worse TMD thresholds, than in $STRC^{-/-}$ or NH children.

Statistical analysis comparing TMD thresholds for the different groups showed a significant main effect of group (hearing method) and modulation rate ($p < 0.0001$ for each) without a group-rate interaction. There was no significant difference between the $STRC^{-/-}$ and NH groups but a significant difference between the latter two groups and the CI group ($p < 0.0001$ for each comparison; Table F).

Table E shows the different average coefficients *b* and *A* for the 3 groups considered. The average coefficients *b* and *A* were obtained after fitting all individual's data with the TMTF equation, to get for each subject, individual coefficients *b* and *A* that we averaged across subjects. The coefficients *b* of the $STRC^{-/-}$ and NH groups are similar, while the coefficient *b* of the CI group is about 5 times lower, meaning a worse temporal resolution, than for the $STRC^{-/-}$ and NH children. The coefficient *A* of the CI children is respectively 19% and 25% lower, meaning a worse sensitivity to temporal modulation than in the $STRC^{-/-}$ and NH groups, while the difference between $STRC^{-/-}$ and NH Children groups is 9%. A main effect of hearing group was not found when comparing coefficient *A* but did for a main effect of hearing group when comparing coefficient *b* ($p < 0.0001$).

The post-hoc analysis conducted on the *b* coefficient (Tukey) found no significant difference between coefficients *b* of the $STRC^{-/-}$ and NH groups. However, coefficients *b* were significantly different between $STRC^{-/-}$ and CI group and between NH and CI children ($p = 0.0385$ and $p = 0.0372$ respectively).

### 3.3. Speech in-noise perception (Figures 4 and 5)

Figure 4 shows adaptive spondee reception thresholds in steady-state noise. The mean SRT in the $STRC^{-/-}$ group was −13.9 dB (+/− 1.46 dB). A previous study carried out by Drennan *et al.* showed a mean SRT of −19.2 dB (+/− 0.75 dB) for NH adults which is significantly better than our $STRC^{-/-}$ population ($p = 0.0008$) (24). These results are consistent with impaired speech in-noise perception in these subjects. However, their results were significantly better than the CI children shown in Jung *et al.* with a mean SRT of −8.5 dB (+/− 3.3 dB) ($p = 0.0001$) (25).

Figure 5 shows mean pediatric AzBio scores for the *STRC*$^{-/-}$ subjects at fixed signal-to-noise ratios. All *STRC*$^{-/-}$ subjects had performance around 50% at −5 dB of SNR so all of them were tested at 0dB of SNR as well. Performance at 0dB of SNR were similar between the *STRC*$^{-/-}$ group and in the NH children from Holder *et al.* with respectively 87.9% and 97.5% of words identified correctly. *STRC*$^{-/-}$ group performance substantially decreased at −5 dB of SNR to 40.1% while the NH children's performance remained high at 85.4% (26). Although reduced relative to the results of NH children, speech understanding in the *STRC*$^{-/-}$ group was significantly better than in the CI adult or children's groups, with performances of 34 and 54% respectively, at +5 dB of SNR (37,38).

## 4. Discussion

We performed psychoacoustic measures and speech in noise perception of subjects with bi-allelic loss of function *STRC* mutations and hence a specific loss of the cochlear amplifier. This work confirms preservation of temporal resolution and suggests impaired frequency resolution as well as demonstrates impaired speech in noise perception compared to the NH listeners.

*STRC* loss-of-function leads to loss of active cochlear frequency selectivity and amplifier function (9,39). The audiometric profile of these patients was already well-known and is strikingly consistent across individuals. Several publications have demonstrated a moderate flat hearing loss, stable across frequencies, patients, and age with normal speech discrimination in quiet (1,6,40,41). Otoacoustic emissions are usually absent (1,5). Since otoacoustic emissions directly reflect the outer hair cells' function, their absence implies non-functional outer hair cells due to lost stereocilin expression. Participants in this study displayed an audiometric profile similar to that described in the literature; including normal speech perception in quiet. Despite the small sample of our cohort, the great stability of this audiometric profile across subjects suggests that our results will generalize to the larger population, including younger children as well as adults, with similar *STRC*$^{-/-}$ genotypes. Determining frequency and temporal resolution through psychophysical adaptative tracking procedures allowed us to more precisely characterize the auditory deficits in this population. Spectral and temporal cue detection abilities play a crucial role in speech-perception, especially in the presence of background noise (42–45).

Our study shows that *STRC*$^{-/-}$ listeners are worse than NH for SRD but not for TMD. However, the SRD thresholds remained better in the *STRC*$^{-/-}$ population compared to the CI group. Impaired cochlear frequency selectivity in the *STRC*$^{-/-}$ group would be expected to lead to imprecise representation of peak locations in the amplitude spectrum of a complex auditory signal and worse SRD thresholds, which depend both on frequency resolution and spectral modulation sensitivity. Frequency resolution can be evaluated independently as the slope of the SMTF (23,46). The significant interaction between hearing group and modulation depth is consistent with an impaired frequency resolution in the *STRC*$^{-/-}$ group but the small sample size limits our ability to definitively prove a better frequency resolution in NH than in *STRC*$^{-/-}$ subjects. Our NH outlier analysis suggests why a larger sample size is likely to provide such definitive proof.

The loss of frequency selectivity in these subjects causes deficits in the ability to filter complex signals. In addition, some studies have shown that at high spectral densities, temporal cues could be used for spectral discrimination (47). This could partly explain the better results in the *STRC*$^{-/-}$ population compared to the CI group in which both spectral and temporal resolution are altered, limiting their ability to use temporal cues to compensate. However, our data suggest that even a passive basilar membrane with a full complement of normal inner hair cells provides better frequency resolution than a cochlear implant.

Frequency resolution was also studied through detection thresholds for a fixed spectral density. Thresholds were, in our population, marked by a significant inter-individual variability and a slightly better detection threshold for 0.5 RPO than 1 RPO. Various publications describing SMTF for a fixed spectral ripple density also report a high interindividual variability at all densities including 0.5 and 1 RPO, in NH listeners and especially in CI listeners with a slight worsening from 0.5 to 1 RPO of spectral density as we found in our work (36,48,49). Our detection thresholds at both 0.5 and 1 RPO were similar to those found in a Sensorineural Hearing Loss (SNHL) group studied by Davies-Venn *et al* who found thresholds, for these densities, of 8 dB (+/−3) and 9 dB (+/−3) respectively while our results were 8.1 dB and 9.2 dB (29). Whether studied by fixed modulation depths or fixed spectral densities, the frequency resolution of the *STRC*$^{-/-}$ group always trended lower when compared to the NH population but better than in the CI group.

Many studies have aimed to describe the impact of cochlear hearing loss on temporal resolution but have mostly focused on presbycusis or pools of subjects with non-specific hearing losses (20,50–53). Their key conclusion is that hearing loss is associated with both temporal and spectral processing deficits. To our knowledge, this is the first study reporting psychoacoustic measures with isolated loss of cochlear frequency selectivity and preservation of temporal resolution in hearing loss with such a specific mechanism. Hearing impairments studied in previous works likely involve several responsible mechanisms including impaired outer and inner hair cell function and potentially comorbid synaptopathy. In contrast, hearing loss due to bi-allelic *STRC* loss-of-function is due to the exclusive dysfunction of the outer hair cells.

A weakness of this study is that the subjects were not matched between the different groups. This results from the fact that the groups belong to different projects, each carried out prospectively in our lab, but over different periods of time. The low number of subjects in each of the groups did not allow matching. However, by using identical methods in the same laboratory, any bias is likely limited. Furthermore, the bi-allelic loss of function of the STRC gene leads to stable phenotypes over time and between subjects, limiting the consequences of both an absence of matching and the extraction of data from previous studies.

The identification of a specific psychoacoustic profile corresponding to the loss of the cochlear amplifier could help to better understand the hearing consequences of mutations in other genes, such as *TECTA*. This gene encodes alpha tectorin, a glycoprotein which is the main component of the tectorial membrane (54). Homozygous *TECTA* knockout leads to a lack of connection between the tectorial membrane and the outer hair cells, and expected

loss of cochlear amplification (55,56). A similar psychoacoustic profile between subjects with the *STRC*$^{-/-}$ mutation and the *TECTA* mutation could confirm this suspicion.

Studying the specific psychoacoustic deficits in listeners with different auditory pathologies is key to a better understanding of suprathreshold deficits. This importance was underlined by Rance *et al.* (2004) who showed that temporal processing and frequency resolution were different between listeners with SNHL and those with auditory neuropathy, suggesting the possibility of specific rehabilitation for specific perceptual deficits (57). With a better understanding of the auditory mechanisms involved in *STRC*$^{-/-}$ subjects, improvements of hearing aid performance may be possible for this group. Hearing aid coding could aim to compensate for impaired spectral detection by increasing the number of frequency channels or narrowing the filter width to match the loss of filtering in a passive cochlea. Such hearing aid processing has been attempted before (58,59), without remarkable results, but never in such a precisely selected population who may uniquely benefit. A caveat would be that since the spectral detection in these subjects has been altered since birth, the central mechanisms of spectral coding may not be adequately developed to take advantage of the improved coding.

Another way to potentially improve the performance of hearing aids in *STRC*$^{-/-}$ patients and specifically their speech understanding in noise, would be to restore the nonlinear compression lost due to dysfunction of the active cochlear mechanism in the outer hair cells of these subjects (10). Through the loss of this mechanism, *STRC*$^{-/-}$ patients may have a diminished ability to benefit optimally from silent gaps in fluctuating background noise. The *STRC*$^{-/-}$ group may only benefit from temporal gaps and not from both temporal and spectral gaps as in NH listeners (60). The ability to fully benefit from these gaps is likely an important mechanism for understanding speech in noise. In addition, loss of the nonlinear compression mechanism may make the use of temporal gaps less effective in *STRC*$^{-/-}$ subjects, as is the case in other subjects with cochlear hearing loss (61). Restoring nonlinear compression could ameliorate this problem.

The *STRC*$^{-/-}$ mutation is probably underdiagnosed in the general population (62). Indeed, it is not typical in clinical practice to carry out systematic genetic screening in the management of this type of moderate and stable SNHL which does not require cochlear implantation. Schuknecht, *et al.* suggested that this audiometric profile was associated with presbycusis due to atrophy of the stria vascularis (63). While that is certainly possible, when seen in childhood or young adults, genetic testing should now be indicated. In the event of an effective improvement in hearing aids for this group of patients, this particular audiometric profile of a stable, flat moderate SNHL with normal speech discrimination could benefit from such “precision audiology”.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Acronym table

| | |
|---|---|
| **DFNB** | Deafness, Neurosensory, Autosomal Recessive |
| **NH** | Normal Hearing |
| **CI** | Cochlear Implant |
| **SRD** | Spectral Ripple Density |
| **RPO** | Ripples Per Octave |
| **SMTF** | Spectral Modulation Transfer Function |
| **TMD** | Temporal Modulation Detection |
| **TMTF** | Temporal Modulation Transfer Function |
| **SRT** | Speech Reception Threshold |
| **SNR** | Signal-to-Noise Ratio |
| **SNHL** | Sensori Neural Hearing Loss |

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## Highlights

- Loss of function of stereocilin (*STRC)* produces deficits of active cochlear frequency selectivity and amplifier functions.
- Frequency resolution seemed impaired in $STRC^{-/-}$ subjects while their temporal resolution was preserved.
- Speech in noise understanding in $STRC^{-/-}$ subjects was impaired compared to normal hearing listeners but remained better than in cochlear implanted listeners.
- Hearing aid modifications, customized for the spectral deficits could potentially improve speech in noise perception in the $STRC^{-/-}$ population.

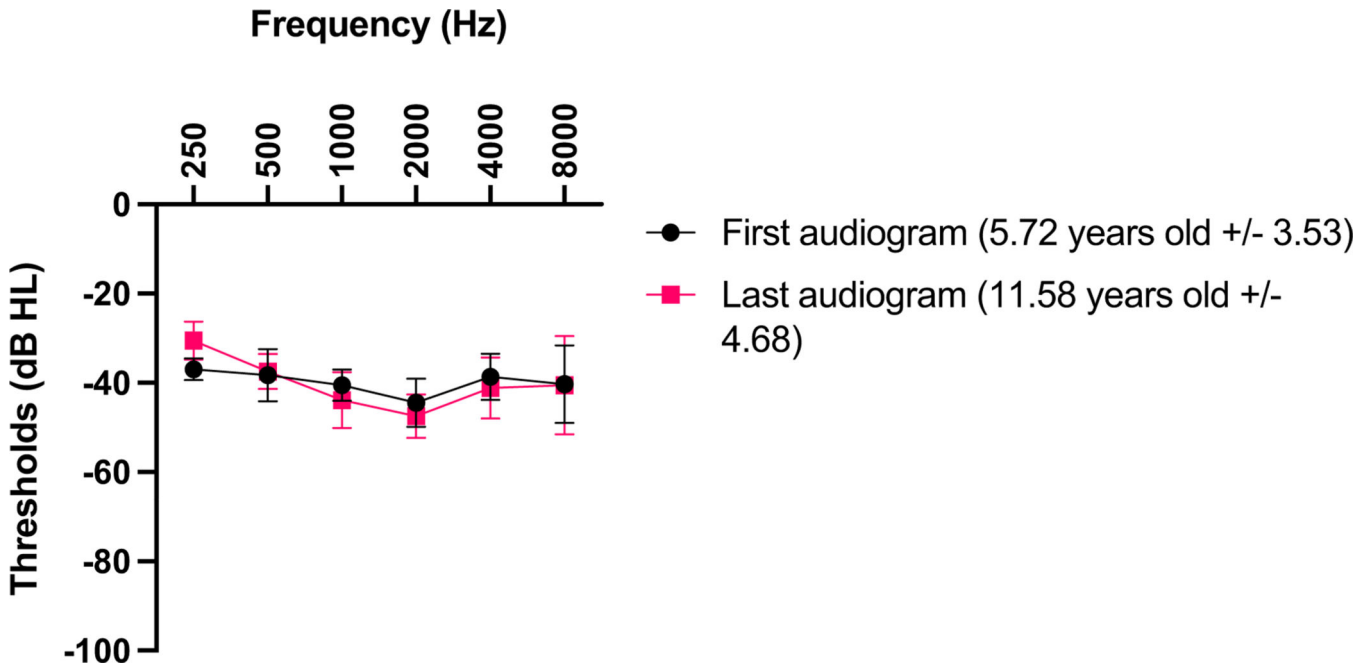


**Figure 1.**

Mean pure tone thresholds of individuals in the *STRC*$^{-/-}$ group, at first and last audiogram. Error bars signify standard deviation. Mean age (+/−SD) of audiogram realization are indicated in legend (N=9)

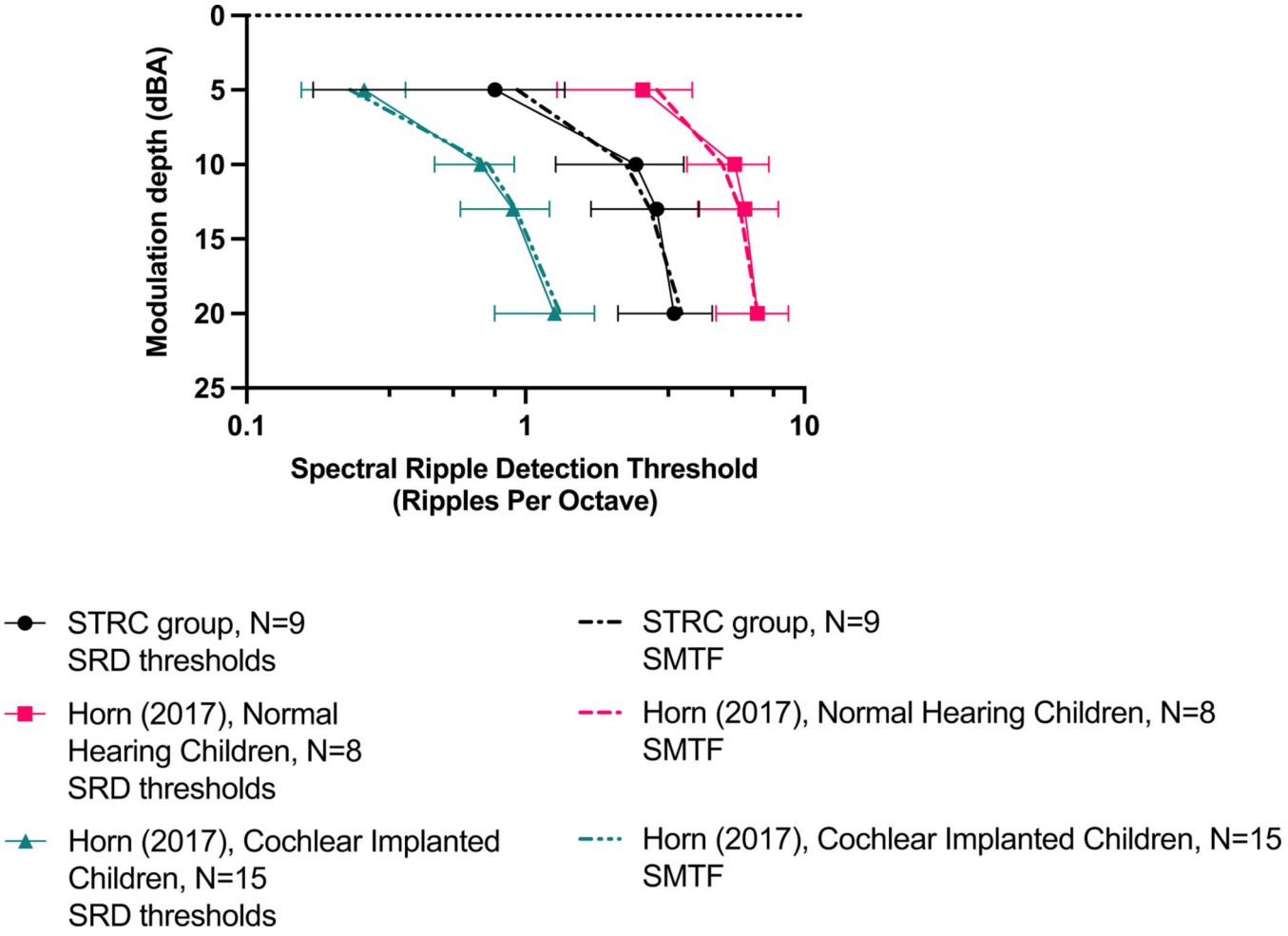


**Figure 2.a.**

Mean spectral ripple detection (SRD) threshold (solid lines with symbols) and Spectral Modulation Transfer Function fitted from mean SRD thresholds (dashed lines without symbols) (x-axis log 10 scale) as a function of ripple depth (y-axis) for $STRC^{-/-}$ group, NH children and CI children. Error bars signify 95% confidence interval. Data for NH and CI children were extracted from Horn *et al.* (23).

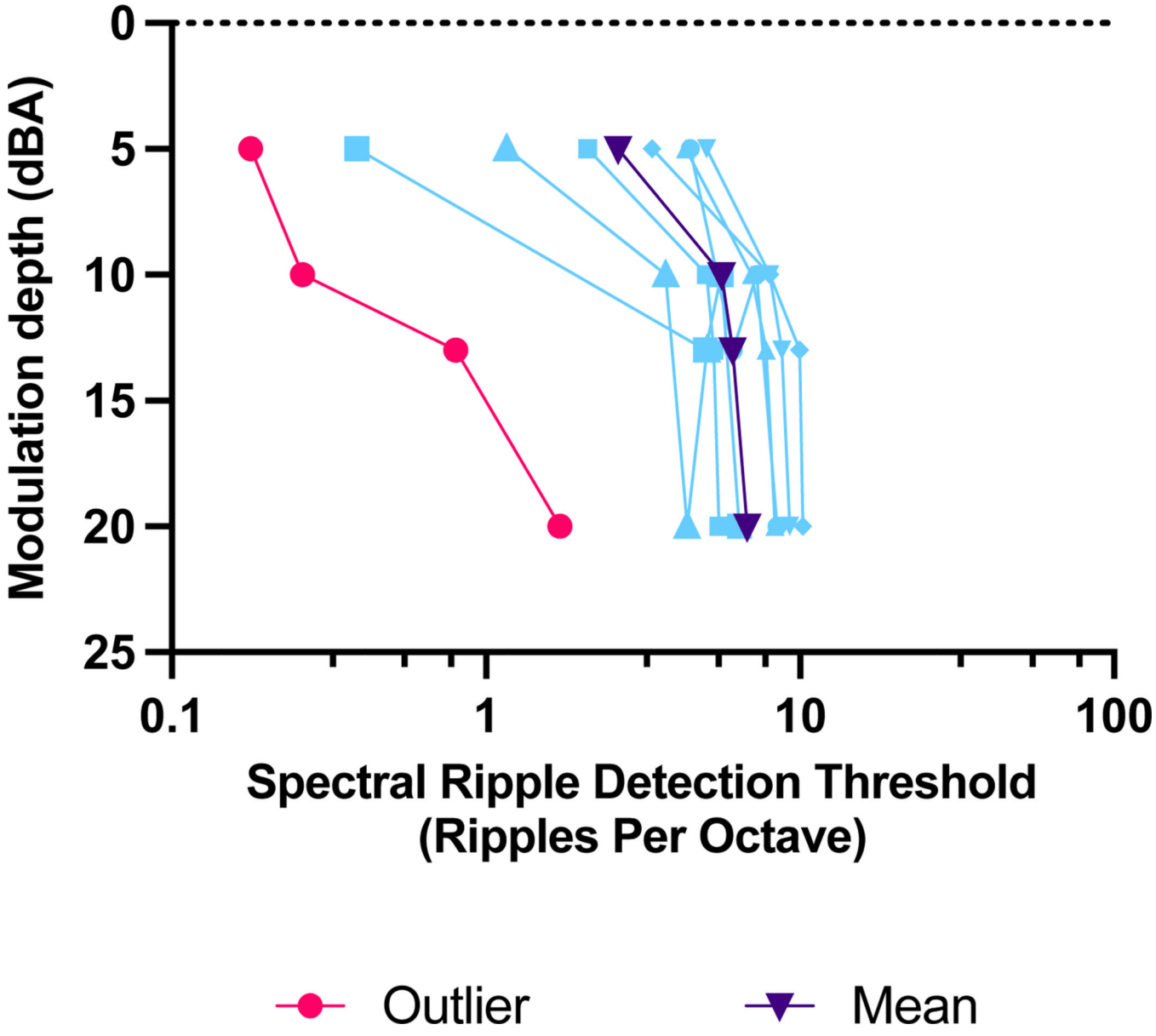


**Figure 2.b.**

Individuals and mean SRD thresholds (log-10 x-axis) as a function of ripple depth (y-axis) for the NH children. The outlier subject's curve is colored in pink, the mean SRD thresholds is colored in purple, and all other NH subjects' curves are colored in blue.

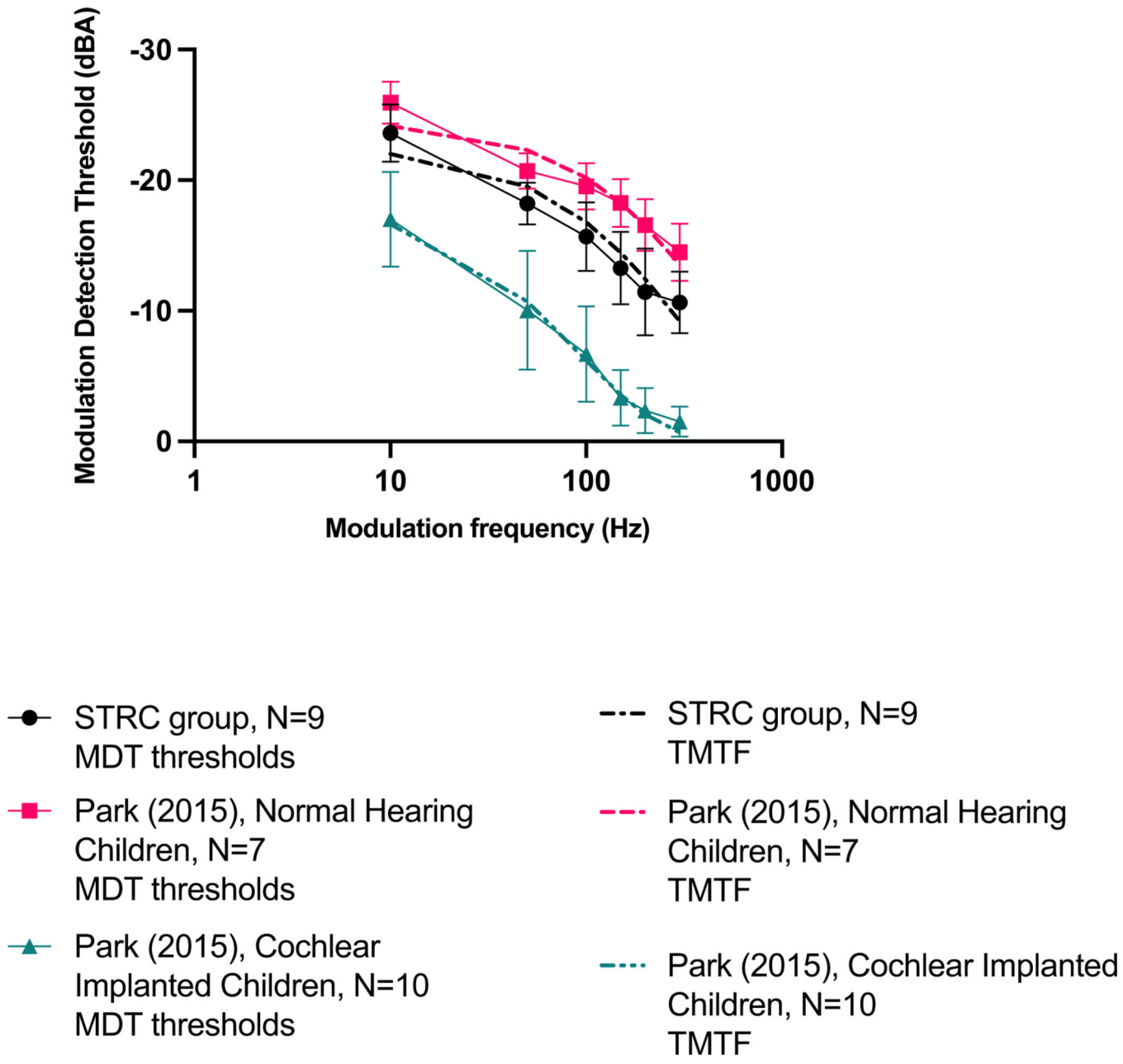


**Figure 3.**

Mean temporal modulation detection (TMD) thresholds (solid lines with symbols) and Temporal Modulation Transfer Function fitted from mean TMD thresholds (dashed lines without symbols) as a function of modulation frequency (log 10 scale on x-axis) for *STRC*$^{-/-}$ group, NH children and CI children. Error bars signify 95% confidence interval. Data for NH and CI children were extracted from Park *et al.* (22).

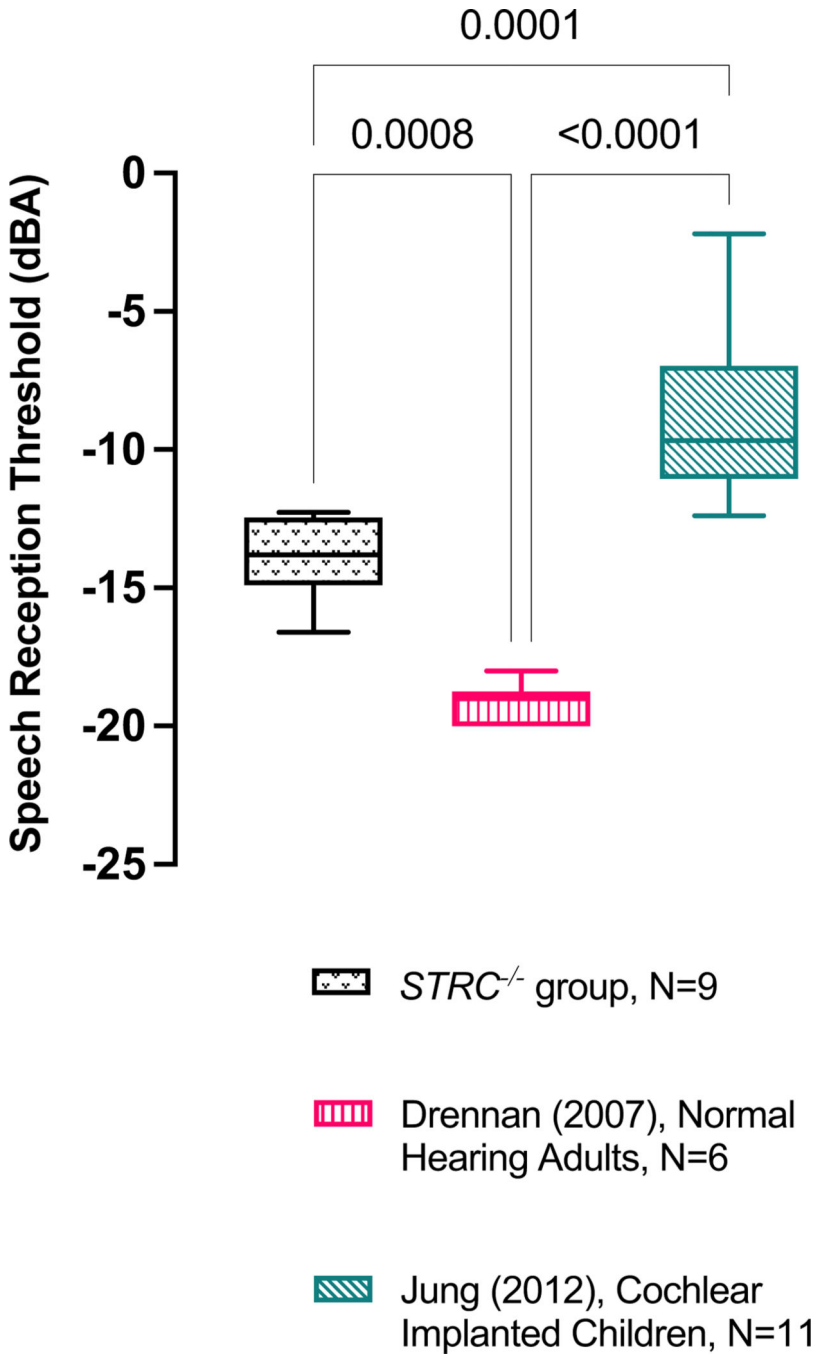


**Figure 4.**

Speech reception thresholds for the Spondee words task for *STRC*$^{-/-}$ group, NH adults and CI children. Boxes indicate 25, 50, and 75 quartiles. Error bars signify standard deviation. Data for NH adults and CI children were extracted from Drennan *et al.* and Jung *et al.* (24,25)

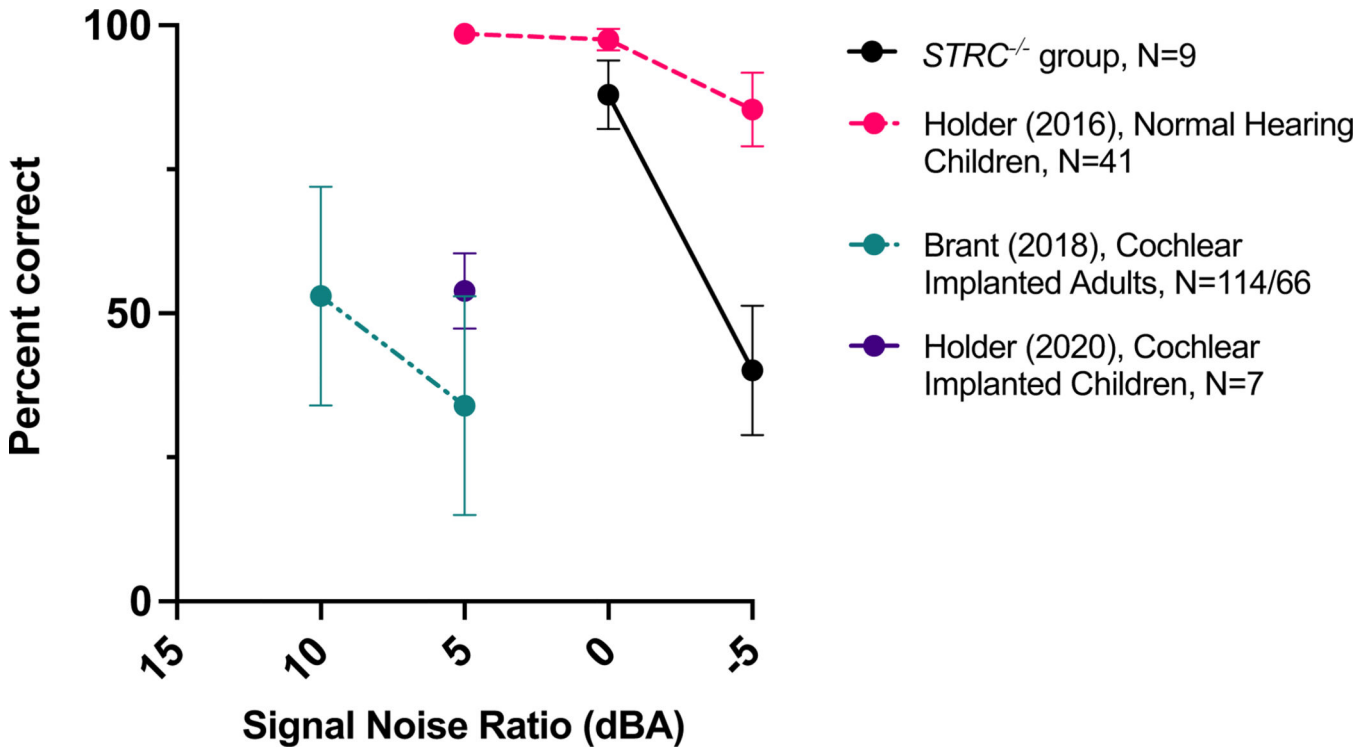


**Figure 5.**

Pediatric AzBio performance at +10/+5/0/−5dB of SNR for *STRC*$^{-/-}$ group, NH children and CI adults and children. Error bars signify standard deviation. Data for NH children were extracted from Holder *et al.* (2016), data for CI adults and children were extracted from respectively Brant *et al.* and Holder *et al.* (2020) (26,37,38).

**Table A.**

*STRC*$^{-/-}$ population characteristics (N=9).

| **Characteristics** | ***STRC*$^{-/-}$ group (N=9)** | **%** |
|---|---|---|
| **Gender at birth** | | |
| Male | 4 | 44.4 |
| Female | 5 | 55.6 |
| **Mean age at diagnosis** in years (SD) | 4.05 (+/− 2.44) | |
| **Mean age at hearing aid fitting** in years (SD) | 4.87 (+/− 2.61) | |
| **Mean Pure Tone Average on first audiogram** in dB (SD) | 39.8 (+/−3.4) | |
| **Mean Pure Tone Average on last audiogram** in dB (SD) | 40.2 (+/− 4.5) | |

**Table B.**

*STRC*$^{-/-}$, NH and CI population characteristics (22,23)

| **Characteristics** | ***STRC*−/− group (N=9)** | **NH group (Horn, 2017) (N=8)** | **CI group (Horn, 2017) (N=15)** | **NH group (Park, 2015) (N=7)** | **CI group (Park, 2015) (N=10)** |
|---|---|---|---|---|---|
| **Gender at birth** | | | | | |
| Male | 4 (44.4) | 6 (75) | 8 (53.3) | | |
| Female | 5 (55.6) | 2 (25) | 7 (46.7) | | |
| **Mean age at inclusion** in years (range) | 12.5 (7–22) | 12.65 (10–14) | 12.8 (7–15) | 11.1 (8–4) | 11.9 (7–16) |

**Table C.**

Coefficient A and b for each group in the SMTF equation $f(x) = b*Ln(x/A)$ (23).

| Group | b estimate (SD) | A estimate (SD) |
|---|---|---|
| *STRC*$^{-/-}$ (N=9) | 1.95 (1.22) | 3.097 (1.35) |
| NH Children (Horn *et al.*, 2017) | 2.38 (1.11) | 1.20 (1.14) |
| CI Children (Horn *et al.*, 2017) | 0.71 (0.59) | 3.40 (1.39) |

**Table D.**

p-value of ANOVA tests for comparison between *STRC*$^{-/-}$ group and NH and CI children for SRD thresholds, frequency resolution estimated by SMTF coefficient b and sensitivity to spectral modulation estimated by SMTF coefficient A.

| | ***STRC*$^{-/-}$ Spectral Ripple Density discrimination thresholds** | ***STRC*$^{-/-}$ frequency resolution (SMTF coefficient *b*)** | ***STRC*$^{-/-}$ sensitivity to spectral modulation (SMTF coefficient *A*)** |
|---|---|---|---|
| vs NH Children (Horn *et al.*, 2017) | **< 0.0001** | 0.0641 * | 0.549 * |
| vs CI Children (Horn *et al.*, 2017) | **< 0.0001** | **0.0155** | 0.832 * |

* non-significant

**Table E.**

Coefficient A and b for each group in the TMTF equation $f(x) = Ae^{bx}$ (31)

| Group | b estimate (SD) | A estimate (SD) |
|---|---|---|
| *STRC*$^{-/-}$ (N=9) | −0.003 (0.002) | 22.67 (2.05) |
| NH Children (Park *et al.*, 2015) | −0.002 (0.000) | 24.6 (1.18) |
| CI Children (Park *et al.*, 2015) | −0.011 (0.002) | 18.41 (1.12) |

**Table F.**

p-value of ANOVA tests for comparison between *STRC*$^{-/-}$group and NH and CI children for TMD thresholds, temporal resolution estimated by TMTF coefficient *b* and sensitivity to temporal modulation by TMTF coefficient *A*.

| | ***STRC*$^{-/-}$ Temporal Modulation Detection Thresholds** | ***STRC*$^{-/-}$ temporal resolution (TMTF coefficient *b*)** | ***STRC*$^{-/-}$ sensitivity to temporal modulation (TMTF coefficient *A*)** |
|---|---|---|---|
| vs NH Children (Park *et al.,* 2015) | 0.062 * | 0.98 * | 0.73 * |
| vs CI Children (Park *et al.*, 2015) | **< 0.0001** | **0.0385** | 0.678 * |

* non-significant