

Accepted Manuscript

Improved interaural timing of acoustic nerve stimulation affects sound localization in single-sided deaf cochlear implant users

J. Seebacher, A. Franke-Triegeer, V. Weichbold, P. Zorowka, K. Stephan



PII: S0378-5955(18)30172-2

DOI: <https://doi.org/10.1016/j.heares.2018.10.015>

Reference: HEARES 7638

To appear in: *Hearing Research*

Received Date: 24 April 2018

Revised Date: 11 September 2018

Accepted Date: 26 October 2018

Please cite this article as: Seebacher, J, Franke-Triegeer, A, Weichbold, V, Zorowka, P, Stephan, K, Improved interaural timing of acoustic nerve stimulation affects sound localization in single-sided deaf cochlear implant users, *Hearing Research*, <https://doi.org/10.1016/j.heares.2018.10.015>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Improved interaural timing of acoustic nerve stimulation affects sound localization in single-sided deaf cochlear implant users

J Seebacher¹, A Franke-Trieger², V Weichbold¹, P Zorowka¹, K Stephan¹

¹Department for Hearing, Speech and Voice Disorders, Medical University of Innsbruck, Austria

²Saxonian Cochlear Implant Center, Department of Otorhinolaryngology, Technical University of Dresden, Germany

Corresponding Author:

Josef Seebacher, PhD
Department for Hearing, Speech and Voice Disorders
Medical University of Innsbruck
Anichstrasse 35
A-6020 Innsbruck
Austria

Abstract

The main impairment associated with single-sided deafness (SSD) is the loss of binaural hearing. Currently, the most effective treatment to compensate for this deficit is to supply patients suffering from SSD with a cochlear implant (CI) in the deaf ear. With this approach binaural hearing abilities can be restored to a certain extent, which is expressed in an improvement in such patients with regard to sound source localization and speech comprehension in noise after receipt of a CI. However, binaural performance of these listeners does not reach the level of normal-hearing listeners. One of the reasons for this might be that the *electrical stimulation via CI* and the *physiological stimulation via the intact ear* are not synchronized: the CI transmits the information to the auditory nerve with different timing than does the intact inner ear. As a result, there is a timing mismatch of the information transfer between the left and the right side, which may account for the limited binaural performance. The effective mismatch in timing depends on the CI system because of different stimulation strategies implemented in devices from different manufacturers. For the particular CI device used in this study (MED-EL Mi1000/Mi1200) electrical stimulation led to faster activation of the auditory nerve than natural for a wide frequency range. In particular, electrical stimulation was about 1 to up to 2 milliseconds ahead of time for frequencies above 1.5 kHz. Hence, it was hypothesized that information transfer between the left and the right ear can be tuned by delaying the CI signal. The goal of the present study was to investigate whether such a delay in the CI signal affects binaural performance of CI users with SSD. For this purpose, sound source localization and speech perception in noise were tested in a sample of 12 CI users with SSD (mean age 51 ± 12 years). The tests were performed for four different delay times of the CI signal applied spontaneously (0.5, 1, 2 and 4 milliseconds) and for the base line condition "no delay" in the CI signal (i.e. everyday use). It was found that delaying the signal had a significant impact on sound source localization. Speech perception in noise was affected, but less pronounced than was sound localization. Regarding sound source localization, a signal delay of 1 millisecond applied to this particular CI device produced the best performance in our patients. It is concluded that improving the synchronization between the CI-transferred signal and the naturally transferred signal could increase binaural hearing performance in CI users with SSD.

Keywords

single-sided deafness; sound localization; interaural timing; cochlear implant; speech in noise; binaural hearing.

Introduction

Single-sided deaf (SSD) patients perceive the acoustic environment with only one ear. In consequence, their auditory system cannot make use of binaural information, which results in substantially degraded sound source localization and decreased speech understanding in noise. In recent years a number of SSD patients were supplied with a cochlear implant (CI) in order to restore binaural hearing. Studies have shown that this approach produces some improvement both in speech understanding in noise and in sound source localization [Rahne & Plontke, 2016; Grossmann, et al., 2016, Doege, et al. 2017]. Overall, the binaural performance of these listeners is comparable to that of bilateral cochlear implant users as well as cochlear implant users with hearing preservation, who score around $20^\circ - 30^\circ$ in terms of angular localization error [Dorman et. al., 2016]. By comparison, listeners with normal hearing achieve an angular accuracy of about 6° , which is not yet reached by CI users with SSD. This indicates that these patients still lack specific auditory information derived from true binaural interaction such as the summation effect and the squelch effect [Doege, et al. 2017].

Binaural hearing requires the auditory system to precisely detect small differences between the two signals that come from the left and the right ear and to integrate them into binaural information. In CI users with SSD integration of these signals may be impeded. In these patients, the acoustic information is delivered in two different ways: via *electrical* stimulation of the auditory nerve on one side and via *physiological* activation of the auditory nerve through the hair cells on the normal-hearing side. The different paths of delivery can cause a mismatch between the two signals, such that the auditory system fails to convert them into reasonable binaural information.

One possible mismatch is that of a divergent tonotopy, resulting in different pitch perception. The effective pitch perceived through stimulation with CI depends on the position of the CI electrodes in the cochlea as well as the assigned frequency bands. Both of these interacting factors should match the natural tonotopy of the human cochlea to provide a natural pitch perception for the CI user. In the case of CI users with SSD a mismatch in tonotopy on the CI side results in different pitch perception in the implanted ear and in the ear with normal hearing [Schatzer, et al. 2014]. Some modification of pitch perception in CI users is possible by modification of the temporal pattern of the electrical stimulation, which was shown e.g. in a fundamental study by Carlyon, [Carlyon & Deeks, 2013]. A more recent study showed that pitch perception with a CI can, to a certain extent, be modified by tuning the CI stimulation rate [Rader, et al., 2016]. Current CI systems do not yet offer this possibility, but in future devices this strategy may permit some adjustment to make pitch perception by CI users more natural. Particularly in CI users with SSD, pitch matching between the implanted ear and the normal-hearing ear may be relevant, because these listeners are able to compare their natural pitch perception with the CI. Another issue with electrical stimulation of the auditory nerve is the smaller dynamic range as compared to natural acoustic hearing. This results in steeper growth of the perceived loudness in the CI ear and potentially impacts binaural hearing in single-sided deaf listeners.

Among these factors, timing of the stimulation of the auditory nerve on the left and the right side may be incorrect. This mismatch is due to the processing of the acoustic signal in the CI system, which leads to a time

shift in stimulation of the auditory nerve in the CI ear as compared to physiological stimulation through the hair cells of the intact ear [Francart & McDermott, 2013]. The problem has been termed “temporal synchronisation problem”. The amount of desynchronisation depends on the stimulation strategy, which differs between manufacturers. Evidence for the temporal synchronisation problem was recently found with auditory brainstem measurements (ABR) in CI patients (*Implant Type: MED-EL, generation Mi1000 and Mi1200*) with a contralateral normal-hearing ear [Zirn, et al. 2015]. In this study, ABR wave V latencies were measured once for electrical stimulation with CI and once for physiological acoustic stimulation in the intact ear in the same patient. The outcome was a deviation in these wave V latencies, which suggested that low frequencies were transmitted to the neural structures more slowly than physiologically, while high frequencies gave rise to faster activation of the neural structures. For the particular CI system employed in the study, time shifts were about one millisecond for frequencies below 1 kHz and up to two milliseconds for frequencies above 1.5 kHz, whereby the effective time shifts are the sum of the processing delays in the CI and the physiological latencies of brainstem responses [Zirn, et al. 2015]. Considering that the auditory system of a normal-hearing person is able to detect interaural time differences (ITD) in the range of *microseconds* for evaluation of binaural information (Blauert et al 1997), a time difference in the range of *milliseconds* almost certainly affects binaural processing.

Regarding sound localization, ITDs are a dominant binaural cue in normal-hearing listeners, while in CI patients with SSD the ability to detect ITDs is limited and hence these patients rely on ILDs. This is supported by results from Dorman and co-workers [Dorman et al., 2015], who found poor performance in CI patients with SSD when localizing low-frequency sounds providing only ITD cues. In fact, electrical stimulation through the CI delivers primarily the information constituting the envelope of the acoustic signal to the neural system, assuming that ILDs are represented in the electrical stimulation patterns. However, it is likely that a serious mismatch in timing also affects the perception of ILDs, because sound levels in the ears are compared at wrong instants of time. In actual fact, both the perception of ITDs and the perception of ILDs are affected by the inaccurate temporal synchronisation between cochlear implant and normal hearing in CI users with SSD. As a result, the binaural performance of these listeners is limited.

From this assumption it is hypothesized that synchronization precision has a significant impact on binaural performance in CI users with SSD. Hence, the goal of the study was to improve synchronisation between CI and normal hearing in these patients. Because the effective frequencies for perceiving ILDs were transmitted to the neural system by the particular CI devices faster than for natural hearing, this could be achieved by delaying the CI signal. With better synchronisation, it was expected that perception of ILDs will become more natural when applying the “correct” delay to the CI signal. Furthermore, with better ILD perception sound localization may improve in CI patients with SSD and – as separation of speech and noise relies on mechanisms that are similar to sound source localization [Tolnai, et al. 2015] – also speech comprehension in noise.

Methods

Study design

The goal of the study was to investigate the effect that a delay in signal processing in the CI has on the binaural performance of SSD patients. The acoustic signal picked up by the CI microphone was delayed equally across all frequencies. Four different delay times were chosen: $\Delta t_1 = 0.5$ milliseconds, $\Delta t_2 = 1.0$ milliseconds, $\Delta t_3 = 2.0$ milliseconds, and $\Delta t_4 = 4.0$ milliseconds. These delay times were selected based on measurements by Zirn et al., who measured latencies of electrically evoked auditory brainstem responses (EABR) for the same CI systems as investigated in this study. The EABR latencies were affected both by the processing time of the CI devices (*MED-EL generation Mi1000 and Mi1200*) and by the physiological transfer times of the neural signals. In particular, Zirn et al. found that wave V latencies when elicited via electrical stimulation differed between CI and a normal-hearing ear by 1 to 2 milliseconds for frequencies >1.5 kHz [Zirn, et al. 2015]. In the present study the range of the delay times (including a condition with no delay, $\Delta t_0 = 0.0$ milliseconds) was selected, such that it broadly covered these temporal differences.

With each of the delay times Δt_0 to Δt_4 , the patients were tested for speech comprehension in noise and for sound source localization.

Subjects

Twelve adults (mean age: 51 ± 12 years) participated in the study. All of them suffered from SSD and had received a CI in the deaf ear at earliest six months before inclusion in the study. In the other ear, all of them had age-appropriate normal hearing. For subjects at an age of 50 years normal hearing is defined as a pure tone average (PTA-4) of less than 30 dB HL (the standards of age-appropriate pure tone thresholds are summarized in EN ISO 7029). The PTA-4 value was calculated as the mean of the frequencies 0.5, 1, 2 and 4 kHz.

Aided-hearing thresholds with the CI were better than 40 dB HL in all participants. Pure tone audiograms pooled for the normal-hearing ear and aided thresholds for the implanted ear are shown in Figure 1. An asymmetry in pure tone thresholds of about 10 – 25 dB between normal hearing and the CI side was found in all patients. This corresponded to their subjective impression that the hearing in the normal ear was dominant over the hearing in the implanted ear. Despite the overall binaural loudness perception, all participants characterized loudness perception of single tones above hearing threshold as being balanced between the normal-hearing ear and the CI.

Demographical data of the patients are presented in more detail in Table 1. Sudden hearing loss was the cause of deafness in eight patients. One patient lost his hearing after having contracted mumps as a child and another one due to radiation therapy for acoustic neuroma. A further patient had a Mondini malformation in the deaf ear, and in one patient the aetiology of the hearing loss was unknown.

The average duration of implant use was 3.6 ± 1.7 years. Two of the subjects had less than one year's experience with the CI, namely 0.6 and 0.75 years. All subjects were supplied with MED-EL implants of the generation Mi1000 and Mi1200 and audio processors of the type OPUS 2.

All subjects had good experience in performing speech tests in quiet and in noise. The samples' median speech reception score (Freiburg monosyllabic word test in quiet at a presentation level of 65 dB SPL) with the CI-aided ear alone (normal-hearing ear plugged) was 53% (interquartile range: 40% – 68%). With the normal-hearing ear alone (CI-deactivated) scores between 90% and 100% were obtained.

Test setup

The speech and localization tests were conducted in an anechoic chamber in order to provide an undistorted free-field environment. The noise level in the chamber was at least 5 dB below the human hearing threshold at all audible frequencies. At the center of the chamber a circular array of seven loudspeakers was mounted in the frontal hemisphere. The span of the array ranged from -90° to $+90^{\circ}$, with an angular spacing of 30° between the loudspeakers. Installation of the loudspeakers complied with the suggestions for audiological testing of SSD CI users described in the recently issued consensus paper [Van d. Heyning, et al. 2017]. A sketch of the experimental setup is shown in Figure 2. Each subject was seated on a chair placed at the centre of the loudspeaker array, at a distance of about one meter from the loudspeakers. A headrest prevented head movements during the tests and, in addition, all participants were instructed to not move their head. The loudspeakers were driven by a computer-controlled switchable multichannel amplifier. The latter received the stimulus signal from a professional audio interface (RME Fireface UC), which conveniently allowed the stimulus parameters to be adjusted. For calibration of the audio signals standardized noise bursts according to CCITT (Comité Consultatif International Téléphonique et Télégraphique) were used. Sound level measurements were performed with a class 1 sound level meter (NTI Audio XL2).

Delay of the CI signal

For applying the delay to the CI signal the following devices were connected in series (Figure 2): an audio processor, type MED-EL Opus2, a microphone preamplifier, a digital equalizer, an amplifier and a second audio processor, type MED-EL Opus 2. Both audio-processors were worn on the patient's implanted ear. The first one was connected to a microphone preamplifier (MED-EL microphone test device) in order to pick up and amplify the microphone signal from the audio processor. The amplified microphone signal was forwarded to a programmable equalizer (Behringer DEQ 2496), which allowed the microphone signal to be delayed in steps of 0.02 milliseconds, while keeping the spectrum of the signal unchanged. Particular delays in the delay line of the Behringer DEQ2496 equalizer were adjusted remotely by sending MIDI System Exclusive Messages. The delayed microphone signal was fed into the external input of the second audio processor after amplification through a conventional headphone amplifier (Presonus HP4). Finally, the second audio processor was coupled to the patient's implant. The level of the signal delivered to the second audio processor was adjusted in such a way that the microphone signal levels in both audio processors were identical throughout the test. In this way, the patients did not notice any difference in loudness between their own audio processors and the study setup when no signal delay was applied.

Sound Source Localization Testing

To measure sound source localization ability, the subjects had to identify the incident direction of a series of stimuli presented randomly across the loudspeaker array. Stimuli were bursts of speech-shaped noise (CCITT). Each burst was composed of three sequences of noise bursts of 300 milliseconds duration separated by gaps of 200 milliseconds. The total duration of one stimulus was 1.3 seconds; onsets as well as offsets of bursts were ramped in a cosine square fashion at a ramp-up time of 5 milliseconds. Two methods were applied to prevent the subjects from effectively using monaural cues for sound localization: roving sound levels and spectral randomization of the stimuli. Both techniques are particularly important when testing CI users with SSD, who are well trained in using loudness changes due to the head shadow effect for sound localization. The head shadow effect amounts to a loudness difference of up to 7 dB, depending on whether a sound is presented to the deaf or the normal-hearing ear of the listener [Schoen, et al., 2005]. In the current testing procedure sound levels of the stimuli were roved around 70 dB SPL, i.e. sound levels of 65, 70 and 75 dB SPL were used. Moreover, the head shadow effect is more effective at high frequencies. Because of this, single-sided deaf listeners perceive sounds facing the normal-hearing ear much more brightly than sounds presented from the deaf side, which gives these listeners some information on the sound source direction. One possibility for reducing this effect is to actively shape the spectral properties of the stimulus. The spectral randomization method applied in the present experiment followed the guidelines outlined in a consensus paper by Van de Heyning [Van de Heyning, et al. 2017]. In practice, each stimulus was weighted with a non-individualized head-related transfer function that was randomly chosen from either 90° left or 90° right. In this way, stimuli with stronger and weaker brightness were generated to mitigate the head shadow effect and restrict participants to use interaural time and level difference cues for sound localization. Remarkably, most participants immediately noticed the loss of the monaural information.

In total, 84 test stimuli were presented in a single test run (7 loudspeakers x 3 sound levels x 4 repetitions). For each test condition, i.e. for each delay time of the CI signal, one test run was performed. The condition “no delay in CI signal” was repeated at the end of each test series in order to verify test-retest reliability.

Speech Comprehension in Noise

Speech comprehension in noise was measured using the German matrix sentence test “Oldenburg sentence test” (OLSA [Wagener, et al. 1999]). The OLSA test is a widely used tool for measuring speech in noise performance of patients with hearing aids or cochlear implants. Psychometric properties of the OLSA in CI patients are described in [Hey, et al., 2014]. The tests were performed in the configuration SON0, i.e. presentation of speech and competing noise from the front. The procedure of the OLSA measurements followed the guidelines for clinical practice, with 20 sentences presented in a single session. The initial speech sound level for sentence presentation was 70dB, as was the level of the competing noise, which was fixed at 70 dB SPL. As competing noise the standard noise signal of the OLSA speech test, i.e. OLNOISE, was used (see e.g. [Wagener & Brand, 2005]). For this type of noise the expected speech reception threshold (SRT) range for normal-hearing individuals is -7.1 ± 1.1 dB signal to noise ratio (SNR) for measurements at a constant noise level. A difference between two SRTs was considered relevant if it exceeded 2.0 dB SNR. During the test, the speech level was varied in an adaptive procedure according to the patients' responses until the speech

reception threshold (SRT) of 50% intelligibility was reached. For each delay time of the CI signal, one OLSA test session was performed. In keeping with the guidelines of the OLSA test, each participant underwent two training units (2 x 20 sentences) before testing in order to familiarize himself with the testing procedure.

Data Analysis and Statistics

Four measures of sound localization were used: (1) the percentage of correct responses, (2) the angular error, (3) the bias and (4) the localization blur. The percentage of correct responses is given as the number of stimuli to which the correct direction was assigned divided by the number of presented stimuli. This measure reflects the overall performance of a subject in identifying the incident direction of sounds. The angular error is defined as the root mean square (RMS) average of the deviations (in degrees [°] azimuth) between the individually judged sound source positions and the correct ones. Because of the discrete nature of the loudspeaker positions, the angular error was interpreted as a subject's tendency to commit a certain amount of angular error.

The bias of sound localization was calculated as the mean deviation of a subject's responses from the frontal direction across all loudspeakers ("mean signed error"). The bias expresses a constant offset that is inherent in all judgements of a subject. Finally, the localization blur was calculated as the standard deviation of the angular error. The localization blur is a measure of the uncertainty of the responses of a subject. All calculations of the sound source localization measures followed the guidelines outlined by Hartmann, [Hartmann et. al., 1998].

As a measure for speech-in-noise performance, the signal-to-noise ratio (SNR [dB]) for 50% speech intelligibility was used.

The effect of a time delay on the outcome measures was analysed through a repeated measures ANOVA, where the within-subject factor "signal delay" included five conditions (i.e. the five different signal delay times). In the case of significance of the factor, post-hoc t-tests were used to compare particular conditions. For this purpose, the alpha-error level was adapted by Bonferroni correction. The Lilliefors test for normality and Mauchly's test for sphericity were used to check whether the data met the requirements for the ANOVA. For the particular calculations the software package IBM SPSS Statistics Version 24, was used.

Results

Sound source localization: RMS angular error and percent correct scores

The overall performance in sound localization of CI users with SSD is shown in Figure 3. The left panel shows the total percentage of correct judgements for the five tested signal delays. The right panel presents the total RMS angular error, calculated as average over the loudspeakers. The study participants achieved their best performance, i.e. maximum percentage of correct judgments and smallest angular errors, at a tested signal delay of 1 millisecond. In comparison to the condition "no signal delay", correct scores increased from 30% to 44% and the angular error decreased from 39° to 29°. For the larger signal delays of 2 and 4 milliseconds, performance in sound localization progressively decreased. In fact, angular errors and percent correct scores

dropped back to values close to the “no signal delay” condition. For instance at a signal delay of 4 milliseconds correct scores amounted to 35% and the mean angular error increased to 39.5°, which is close to the “no signal delay” condition.

Angular errors at individual loudspeaker positions are shown in five polar plots in Figure 4, each showing one condition of signal delay. In this figure, the localization judgements of patients with CI on the right side were mirrored, which means the data are presented as if all patients had the CI on their left side. Large radii of the radial boxplots indicate large angular errors, while small radii indicate small angular errors (i.e. good sound localization). At all loudspeaker positions angular errors tended to be lower for the tested signal delays of 0.5, 1 and 2 milliseconds as compared to the not delayed situation. This improvement was pronounced for sounds incident from the front section, while to the far left and right directions no significant change in the angular error as compared to the not delayed situation was observed. The smallest angular errors were found at a signal delay of 1 milliseconds at loudspeaker positions of $\pm 60^\circ$. Compared to 0.5 and 1 milliseconds, larger angular errors were observed at a signal delay of 2 milliseconds, but not exceeding the condition of no signal delay. Only at a signal delay of 4 milliseconds were angular errors considerably larger at all loudspeaker positions as compared to the not delayed situation.

Test-Retest reliability was assessed for the condition “no delay in CI signal” in seven out of 11 patients. In these patients the “no delay” condition was tested a second time at the end of the entire test series. Overall, most patients achieved very similar results in the retest. The median score for the difference in RMS angular error between the first and the second test was about 2.8°. Only one patient had a difference of 16.3° between tests, which may indicate a learning effect in this patient. In all other patients the results showed high reproducibility.

Repeated measures ANOVA yielded significance for the factor “signal delay” in both measures. In particular for the angular error: $F(2,091, 20.911) = 6.573$; $p=0.006$ (Greenhouse-Geisser correction applied) and for percent correct scores: $F(4, 40) = 4.193$; $p = 0.006$. Further comparison of the five test conditions (paired-sample t-tests) yielded significant differences between the 0.5 and the 1 millisecond signal delay conditions and the “no delay” condition, indicated in Figure 3.

Sound source localization: localization blur

The localization blur, which is a measure of the uncertainty of sound localization judgements, showed the same trend as the RMS angular error, but in a less pronounced way. At signal delays of 0.5 and 1 millisecond the smallest values for localization blur were achieved, i.e. a median score of $28.1 \pm 7.7^\circ$ and $27.9 \pm 7.3^\circ$, respectively. This value indicates that most subjects missed the correct sound source position by, on average, 30° (that is exactly one loudspeaker off). In the “daily use” condition when no delay was applied to the CI signal, the median score of the localization blur was $31.9 \pm 7.4^\circ$. With larger signal delays, i.e. 2 and 4 milliseconds, the median score for localization blur increased and amounted to $30.0 \pm 7.2^\circ$ and $35.5 \pm 8.2^\circ$, respectively. Despite the fact that there were only small differences in localization blur between the five delay conditions, repeated measures ANOVA yielded significance for the factor “signal delay” also with this measure, $F(4,40) = 4.467$; $p = 0.004$.

Sound source localization: localization bias

Absolute values for the sound localization bias are shown in Figure 5 for each “signal delay” condition. The present group achieved a bias of about 10° on average when using their CI without a signal delay. This might result from a small loudness difference perceived between normal hearing and the CI-aided ear. In the present group aided thresholds (PTA4 average) on the CI side were about 17.5dB lower than on the normal-hearing side. This loudness difference yields a bias of 19°-28° according to calculations by Schoen et al., who found a slope of 1.1° – 1.6° per dB loudness difference in their measurements [Schoen, et al., 2005]. The calculated bias overestimates the measured situation. Above threshold, the loudness difference between CI and normal hearing might be smaller and hence the localization bias.

For the signal delay conditions of 0.5 and 1 milliseconds the present group showed a bias similar to that for the “no delay” condition, i.e. about 10°. For signal delays of 2 and 4 milliseconds a larger bias of up to 20° was observed. Repeated measures ANOVA confirmed that the factor “signal delay” had a significant impact on the bias, i.e. $F(2.428, 24.283) = 11.218$; $p < 0.001$ (Greenhouse-Geisser correction applied).

Speech in Noise Scores

The speech reception thresholds (SRT) measured as signal to noise ratios (SNR) are shown in Figure 6 for the five signal delay conditions. More negative SNR values indicate better performance. The speech reception thresholds observed in our group of SSD CI users were between -4 and -5 dB SNR, which is close to the performance of normal-hearing subjects, who usually achieve speech reception thresholds of -7 to -8 dB SNR in the present setup. In addition, a clear effect of the signal delay on the speech reception thresholds was not found. Speech reception performance was best at delay times of 1 and 2 milliseconds, but, remarkably, also when no delay was applied to the signal. The speech reception thresholds also showed considerable inter-individual differences: while a few participants reached speech reception thresholds close to those of normal-hearing persons in the no delay condition, others performed much worse. Due to the large interindividual variation, the statistical comparison of the mean SNR between different delay conditions (repeated measures ANOVA) did not reveal significance. Hence, the impact of interaural stimulation enhancement on speech perception is apparently less pronounced than on sound source localization.

Discussion

The existence of a mismatch in timing between natural auditory processing in a normal-hearing ear and the processing of acoustic signals in a cochlear implant is obvious. The extent of the timing mismatch mainly depends on the type of speech-coding strategy that is incorporated in the particular cochlear implant device. Certainly, such a timing mismatch impacts binaural hearing of CI users with SSD, but the net effect is yet unknown. Hence the aim of this study was to investigate whether such a timing mismatch affects binaural hearing in these patients and also whether it is possible to compensate for this drawback. For this purpose, the two most important binaural hearing abilities, sound source localization and speech intelligibility in noise, were tested.

Regarding sound localization, all but one of the 12 tested subjects showed a definite ability to localize sound sources when using the CI in the reference condition “no delay in CI signal”. The overall performance of the present group of CI users with SSD in sound localization was similar to that of those described by Dorman et al. [Dorman, et al. 2015]. The key finding of his study was that CI users with SSD are more likely sensitive to interaural level differences (ILD) when localizing sound sources rather than being able to access interaural time differences (ITD). In general, ITDs are effective only at frequencies below 1.5 kHz and normal-hearing listeners are sensitive to ITDs down to 10 μ s. In experiments with dichotic sound presentation of low frequencies it was shown that a full lateral shift is achieved at an ITD of about 600 μ s, which is the maximum ITD usable for sound localization in normal-hearing listeners [Blauert, et al. 1997]. In comparison, the timing mismatch between cochlear implant processing and normal hearing is in the order of a millisecond. Hence, ITD cues are blurred in CI users with SSD. This could be one of the reasons why Dorman et. al. [Dorman, et al. 2015] found a very limited ability to localize low-frequency stimuli in single-sided deaf listeners with CI. Apart from that, Dorman and his coworkers found that sound localization performance of the patients was much better when presenting high-frequency sounds. This indicates that CI users with SSD mainly rely on ILD cues when localizing sound sources. In this respect CI users with SSD behave similar to bilateral CI users, see e.g. [Schoen, et al., 2005]. Considering the reference condition “no delay in CI signal”, this study group achieved their best scores in sound localization at $\pm 60^\circ$ (see Figure 4). At such angles, the interaural difference in sound levels reaches its maximum [Macaulay, et al. 2010], which may explain the good performance of the study participants. Interestingly, all subjects showed larger angular errors at 270° when sound is presented from the far left or right side (data from patients with a CI on the right ear were mirrored). In fact, the subjects showed a tendency to perceive sounds presented from far left (CI side) as if they were shifted slightly to the front. This might be because ILDs alone are not a unique cue for localizing sounds presented from directions ranging from -90° to 90° , because the maximum ILD already occurs at 40° to 70° (depending on frequency) and declines when approaching $\pm 90^\circ$. Hence, sounds presented from the far left or right direction may be perceived as if the source direction were more frontal. Another possible reason might be the absence of the pinna in the CI ear, which degrades sound localization accuracy in the CI ear. Overall, the sound localization performance in the reference condition “no delay in CI signal” supports the view that CI users with SSD are able to perceive ILD cues. However, the question remains how well ILDs are represented along the auditory pathway.

Without the introduction of a delay, i.e. in the “daily use” condition, a timing mismatch between electrical stimulation of the auditory nerve via the CI and acoustic stimulation on the normal-hearing side is evident. This most certainly affects perception of ILDs, because time-shifted signals in the left and the right ear will be converted into a wrong ILD. The binaural processor evaluating ILDs is believed to be located in the brainstem, i.e. in the lateral superior olives [Joris & Yin, 1995]. At this point along the auditory pathway the physiologically encoded sound level of the ipsilateral stimulus is subtracted from the contralateral one. The information is encoded in the discharge rates of the neurons of the lateral superior olives, which are excited for sounds arriving from the ipsilateral ear and inhibited for sounds arriving from the contralateral ear. Thereby, the inputs from the two ears have to be in temporal register; if not, the levels of excitation and inhibition will change and

consequently different ILD information will be generated in the lateral superior olive (LSO) than is present in the stimulus [Tollin, 2003].

The degree of timing accuracy required for accurate evaluation of ILDs varies in the literature. A more recent study by Brown and Tollin [Brown & Tollin, 2016] argues that temporal integration makes evaluation of ILDs quite robust toward decorrelation of the left and right ear signals. They claim that the window of integration may be up to 3 milliseconds. In this case a timing mismatch of one or two milliseconds as present in CI users with SSD would not matter at all for binaural hearing abilities. On the other hand, Joris and his co-workers found in physiological measurements that ipsilateral and contralateral signals in the LSO are matched in time quite well in normal-hearing listeners [Joris & Yin, 1995]. The average physiological delays were in the range of 0.2 milliseconds. In another study by Bernstein on discrimination of brief changes in binaural cues, such as an interaural intensity difference, the time constants of a corresponding integration window were found to be one tenth of a millisecond [Bernstein et. al., 2001]. In other theoretical models of ILD computation for pure tone stimuli in the lateral superior olive by Bures an integration window of 200 microseconds was chosen to achieve results comparable to physiological measurements [Bures & Marsalek, 2013]. Moreover, very recent research results on the brainstem's lateral superior olive and its impact on localizing high-frequency sounds show that principal LSO neurons, which are the most numerous in this nucleus, respond mainly to sound onset, suggesting an importance for timing [Franken et. al., 2018]. In view of these findings a timing mismatch of a millisecond between ipsi- and contralateral signals, as present in CI users with SSD, might matter.

Indeed, in the sample of single-sided deaf cochlear implant patients tested in this study a time shift in the signal on the cochlear implant side had a significant effect on sound localization abilities. The best performance in sound localization by the participants was achieved for a delay of the cochlear implant signal by about one and two milliseconds. In this condition RMS angular errors were considerably lower. Further sound localization deteriorated again at a signal delay of four milliseconds, where the angular error approached the value of the not delayed situation. This goes along with the measurements made by Joris, which show a decline in the ILD cue when the interaural delay becomes too large [Joris & Yin, 1995].

One limitation of the study is the acute application of the signal delay. All the patients relearned sound localization after receiving their CI by using the "daily use" adjustment of the audio processor. Hence, patients were used to their "false timing" when evaluating binaural cues to localize sound sources. In the present experiment the signal delays were applied shortly before the test runs, which gave the patients only a few minutes to familiarize themselves with the new hearing situation. Thus, in the long run the sound localization abilities of these patients may change further when applying a signal delay to the CI system, which may be investigated in a future study.

A further limitation of the study is the fact that ILDs may have been influenced by the CI audio processor. To transfer the delayed signal to the cochlear implant the external input of the audio processor was used. In this case the microphone signal was strongly attenuated, but not completely switched off. Thus, the onset of the sound stimuli, which is of particular importance for sound localization, was possibly altered. Measurements show that the microphone signal was reduced by about 40dB while the external input was connected. The

stimuli were roved around 70 dB and the threshold of hearing on the CI side was about 30 dB (see Figure 1). Hence, subjects might have been able to perceive a noise burst almost at the level of their hearing threshold, which may have affected their sound localization ability.

The effect of the delay in the CI signal on speech in noise performance showed a trend different from that for the sound localization results. A statistically significant change in SRT between test conditions was not seen. Most notably, the inter-individual variability increased with prolonged delay of the CI signal as illustrated by the boxplots in Figure 6. In particular, for signal delays of 2 and 4 milliseconds the SRT range was about twice as large as for all other tested signal delays. This indicates an increasing uncertainty in speech perception in noise with prolonged delay of the CI signal. An improvement in SRT at particular signal delays as for sound localization was clearly not seen, but all of these CI patients already had quite good speech reception thresholds in the “no delay” condition. The latter observation may be due to learning effects originating from the experience of the CI users in the “no signal delay” (daily use) condition: the patients may have learned to optimize their speech perception in this condition.

No effect on perception of loudness was found. When subjects had to compare two noise bursts, the second of which was delayed by 0.5 to up to 4 milliseconds, they could not notice any difference in loudness perception. This is in line with the bias, which did not change up to signal delays of 2 milliseconds as compared to the not delayed situation. At the largest measured signal delays of 4 milliseconds the bias started to increase and the subjects perceived the stimuli differently. However, in this situation not all subjects reported a change in loudness, but instead the occurrence of reverberation.

Overall, a delay in the CI signal of about one millisecond had a significant effect on sound localization in CI users with SSD when using the implants investigated. This result is in line with the findings of Zirn et. al., who found that auditory brainstem potentials elicited by high-frequency sounds appear approximately one millisecond ahead of time for these types of implants as compared to normal hearing [Zirn et al., 2015]. Thus, an appropriate delay in the CI signal may compensate at least partly for the asynchronous information transfer of high-frequency sounds to the neural system in patients with SSD. If the signal delay becomes too large, it further enhances the amount of desynchronization of the two signals in the ears, which was expressed in a worsening of binaural performance by these patients. In view of these results, timing of the CI signal seems to matter in CI users with SSD, at least when considering sound source localization.

An adjustable delay in the CI signal may be a promising option for future CI systems. This would at least improve sound localization performance. Such a feature could be even more important in case of bimodal supply with hearing aid and CI, where much larger timing differences were measured [Zirn et al., 2015].

Conclusion

A signal delay in the pre-processing of a CI audio processor affects binaural hearing performance of CI users with SSD. In particular, in sound localization an improvement was seen at certain signal delays in these patients. This suggests that perception of ILDs may have been more accurate because of better synchronization

of high frequencies, at which ILDs are effective. The effect of the signal delay on speech intelligibility in noise was that performance by the patients deteriorated for larger signal delays. No improvement at particular signal delays, as for sound localization, was seen. No effect of the signal delay on perception of loudness was found in this group of CI users with SSD. Nonetheless, adjustable stimulation timing of the CI might be a useful option for improving binaural hearing performance of CI patients with single-sided deafness.

Acknowledgments

We acknowledge the audiological group from the Cochlear Implant Center in Dresden for their support by recruiting patients suitable for participation in this study.

Conflicts of interest

The authors report no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] Zirn, S., Arndt, S., Aschendorff, A., Wesarg, T., 2015. Interaural stimulation timing in single sided deaf cochlear implant users. *Hear Res* 328, 148-56
- [2] Wagener, K., Brand, T., Kühnel, V., Kollmeier, B., 1999. Entwicklung und Evaluation eines Satztests in deutscher Sprache I–III: Design, Optimierung und Evaluation des Oldenburger Satztests. *Z Audiol* 38, 1–3, 4–15, 44–56, 86–95
- [3] Schatzer, R., Vermeire, K., Visser, D., Krenmayr, A., Kals, M., Voormolen, M., Van de Heyning, P., Zierhofer, C., 2014. Electric-acoustic pitch comparisons in single-sided-deaf cochlear implant users: Frequency-place functions and rate pitch. *Hear Res* 309, 26-35
- [4] Francart, T., McDermott, H., 2013. Psychophysics, Fitting, and Signal Processing for Combined Hearing Aid and Cochlear Implant Stimulation. *Ear and Hearing* 34, 685-700
- [5] Van de Heyning, P., Távora-Vieira, D., Mertens, G., Van Rompaey, V., Rajan, G.P., et al. 2017. Towards a Unified Testing Framework for Single-Sided Deafness Studies: A Consensus Paper. *Audiology Neuro-Otology* 21, 391-398
- [6] Dorman, M.F., Zeitler, D., Cook, S.J., Loisel, L., Yost, W.A., Wanna, G.B., Gifford, R.H., 2015. Interaural Level Difference Cues Determine Sound Source Localization by Single-Sided Deaf Patients Fit with a Cochlear Implant. *Audiol Neurotol* 20, 183–188
- [7] Schoen, F., Mueller, J., Helms, J., Nopp, P., 2005. Sound Localization and Sensitivity to Interaural Cues in Bilateral Users of the Med-El Combi 40/40+Cochlear Implant System. *Otol Neurotol* 26, 429–437
- [8] Bures, Z., Marsalek, P., 2013. On the precision of neural computation with interaural level differences in the lateral superior olive. *Brain Res* 1536, 16-26
- [9] Brown, A.D., Tollin, D.J., 2016. Slow Temporal Integration Enables Robust Neural Coding and Perception of a Cue to Sound Source Location. *J Neurosci* 36, 9908-21
- [10] Tollin, D.J., 2003. The Lateral Superior Olive: A Functional Role in Sound Source Localization. *The Neuroscientist* 9, 127-43
- [11] Doege, J., Baumann, U., Weissgerber, T., Rader, T., 2017, Single-Sided Deafness: Impact of Cochlear Implantation on Speech Perception in Complex Noise and on Auditory Localization Accuracy. *Otol Neurotol* 38, 563-69
- [12] Rader, T., Doege, J., Adel, Y., Weissgerber, T., Baumann, U., 2016. Place dependent stimulation rates improve pitch perception in cochlear implantees with single-sided deafness. *Hear Res* 339, 94-103
- [13] Tolnai, S., Dolležal, L.V., Klump, G.M., 2015, Binaural cues provide for a release from informational masking. *Behav Neurosci* 129, 589-98
- [14] Joris, P.X., Yin, T.C., 1995, Envelope Coding in the Lateral Superior Olive. I. Sensitivity to Interaural Time Differences. *J Neurophysiol* 73, 1043-62
- [15] Macaulay, E.J., Hartmann, W.M., 2010, The acoustical bright spot and mislocalization of tones by human listeners. *J Acoust Soc Am* 127, 1140-49
- [16] Hey, M., Hocke, T., Hedderich, J., Müller-Deile, J., 2014. Investigation of a matrix sentence test in noise: Reproducibility and discrimination function in cochlear implant patients. *Int J Audiology* 53, 895–902.
- [17] Grossmann, W., Brill, S., Moeltner, A., Mlynski, R., Hagen, R., Radeloff, A., 2016. Cochlear Implantation Improves Spatial Release From Masking and Restores Localization Abilities in Single-sided Deaf Patients. *Otol Neurotol* 37, 658–664
- [18] Rahne, T, Plontke S.K., 2016, Functional Result After Cochlear Implantation in Children and Adults With Single-sided Deafness. *Otol Neurotol* 37, 332-40
- [19] Blauert, J., 1997. *Spatial Hearing: The Psychophysics of Human Sound Localization*. MIT Press

- [20] Hartmann, M.W., Rakerd, B., Gaalaas B.J., 1998. On the source-identification method. *J. Acoust. Soc. Am.* 104, 3546-57
- [21] Wagener, K.C., Brand, T., 2005. Sentence intelligibility in noise for listeners with normal hearing and hearing impairment: Influence of measurement procedure and masking parameters. *Int. J. Audiol.* 44, 144–157.
- [22] Bernstein, L.R., Trahiotis C., Akeroyd M.A., Hartung, K., 2001. Sensitivity to brief changes of interaural time and interaural intensity. *J. Acoust. Soc. Am.* 109, 1604-15
- [23] Franken, T.P., Joris, P.X., Smith, P.H., 2018. Principal cells of the brainstem's interaural sound level detector are temporal differentiators rather than integrators. *eLife* 2018;7:e33854
- [24] Dorman, M.F., Loiselle, L.H., Cook, S.J., Yost, W.A., Gifford, R.H., 2016. Sound source localization by normal hearing listeners, hearing-impaired listeners and cochlear implant listeners. *Audiol Neurootol.* 21(3): 127–131.
- [25] Carlyon, R.P., Deeks J.M., 2013. Relationships between auditory nerve activity and temporal pitch perception in cochlear implant users. *Adv Exp Med Biol.* 787, 363-71

TABLE 1:

Subject	Sex	Age at Test (years)	CI Side	Duration of Implant Use (years)	Aetiology
1	F	27.7	R	3.9	Idiopathic, deafness since childhood
2	F	59.8	R	2.9	Sudden hearing loss
3	F	56.5	L	4.5	Mumps, Parotitis epidemica
4	F	48.3	L	0.8	Sudden hearing loss
5	M	53.2	L	3.5	Sudden hearing loss
6	F	26.0	L	0.6	Mondini malformation of the inner ear, i.e. 1.5 turns. Partial deafness since birth
7	F	50.7	R	2.9	Sudden hearing loss
8	F	55.3	L	4.1	Sudden hearing loss
9	F	52.5	R	3.5	Sudden hearing loss
10	F	58.4	R	6.9	Sudden hearing loss
11	F	62.8	L	4.9	Sudden hearing loss
12	M	61.3	L	5.0	Acoustic neuroma

Table 1: Demographics of the study participants (Abbreviations: F/M...Female/Male; R/L...Right/Left; CI...Cochlear Implant)

Caption Figure 1:

Figure 1: Pure tone hearing thresholds for normal-hearing ear and aided-hearing threshold with CI in patients with single-sided deafness. Audiograms of normal-hearing ears were grouped and plotted on the left panel, while group data for aided hearing thresholds with cochlear implant are shown on the right panel.

Caption Figure 2:

Figure 2: The loudspeaker array for horizontal localization tests in the frontal hemisphere consisted of seven loudspeakers positioned at angles of -90° to 90° with spacing of 30° . The time delay in the cochlear implant signal was adjusted with a system consisting of two OPUS 2 audioprocessors on the patient's implanted ear, a microphone preamplifier and a digital signal processing unit. The volume level of the input signal delivered to the audio-processor, which was coupled to the patient's implant, was adapted to provide the same signal input as the regular microphone of the audio processor.

Caption Figure 3:

Figure 3: Scores for correct sound localization (in percent, left panel) and root mean square angular error (right panel) for signal delays of 0.5, 1, 2 and 4 milliseconds. As reference, the standard condition "CI use with no signal delay" is shown in both plots. Statistically significant differences between conditions are marked with an "**".

Caption Figure 4:

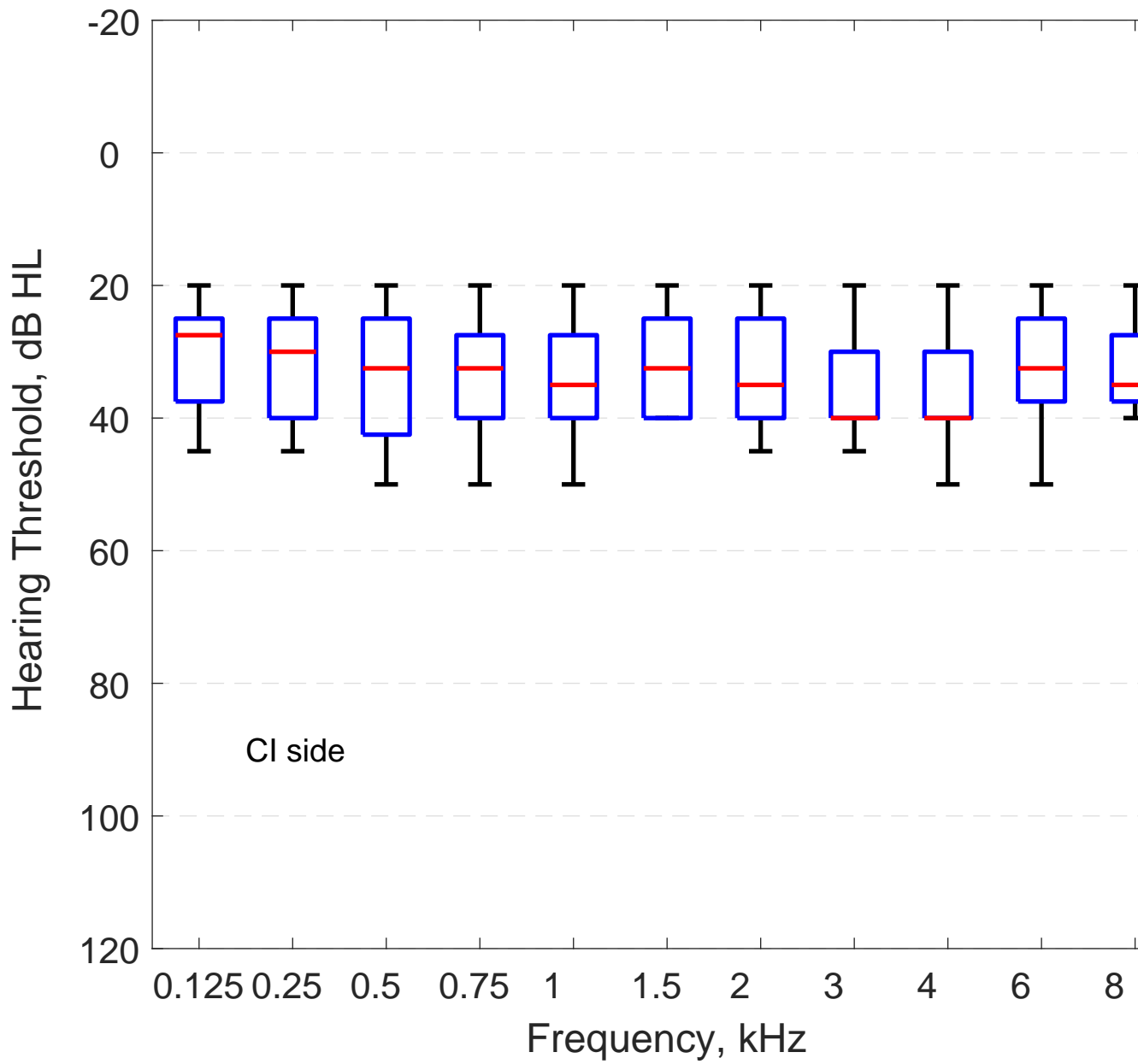
Figure 4: Top panel: loudspeaker-dependent root mean square angular error and corresponding upper and lower quartiles shown for standard usage of the cochlear implant, i.e. no delay was applied to the input signal. Middle panels: Root mean squared angular errors for each loudspeaker position and signal delays of 0.5 milliseconds (left) and 1 milliseconds (right). Lower panels: Root mean squared angular errors for each loudspeaker position and signal delays of 2 milliseconds (left) and 4 milliseconds (right).

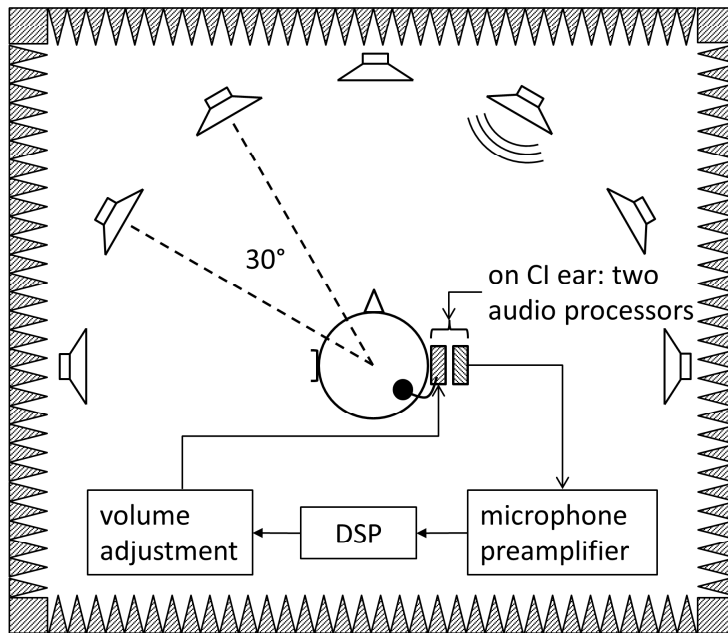
Caption Figure 5:

Figure 5: The group average for the absolute bias of sound localization is shown for all signal delays tested, i.e. 0, 0.5, 1, 2 and 4 milliseconds. Statistically significant differences between conditions are marked with an *.

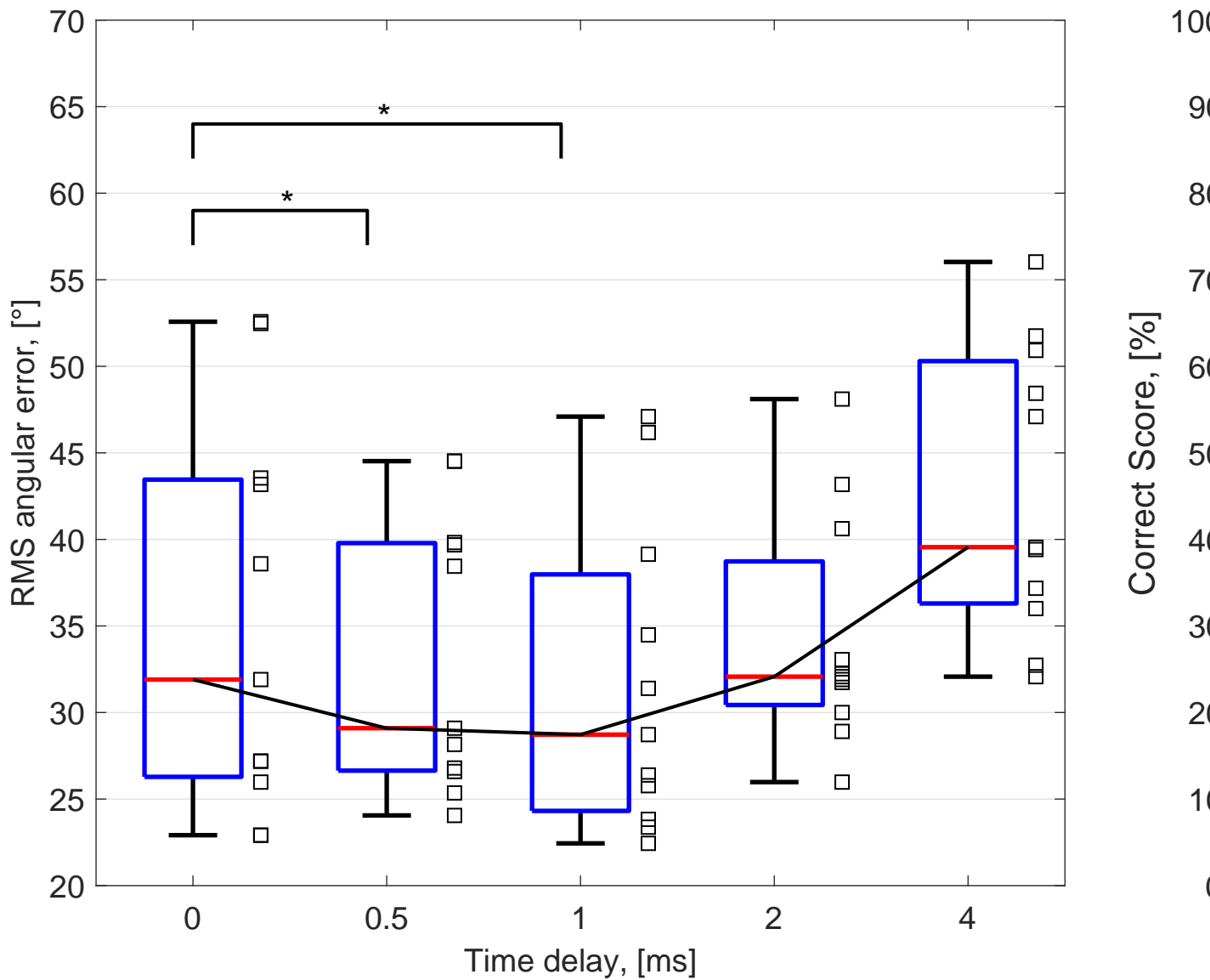
Caption Figure 6:

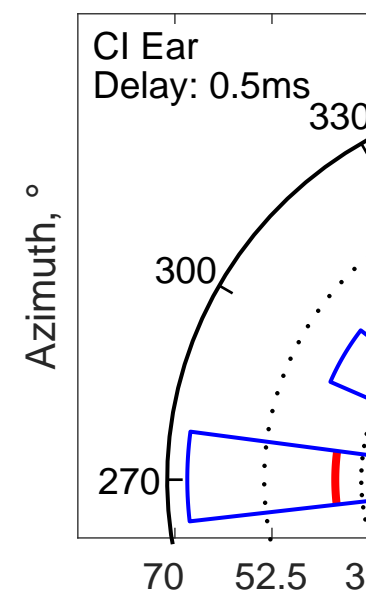
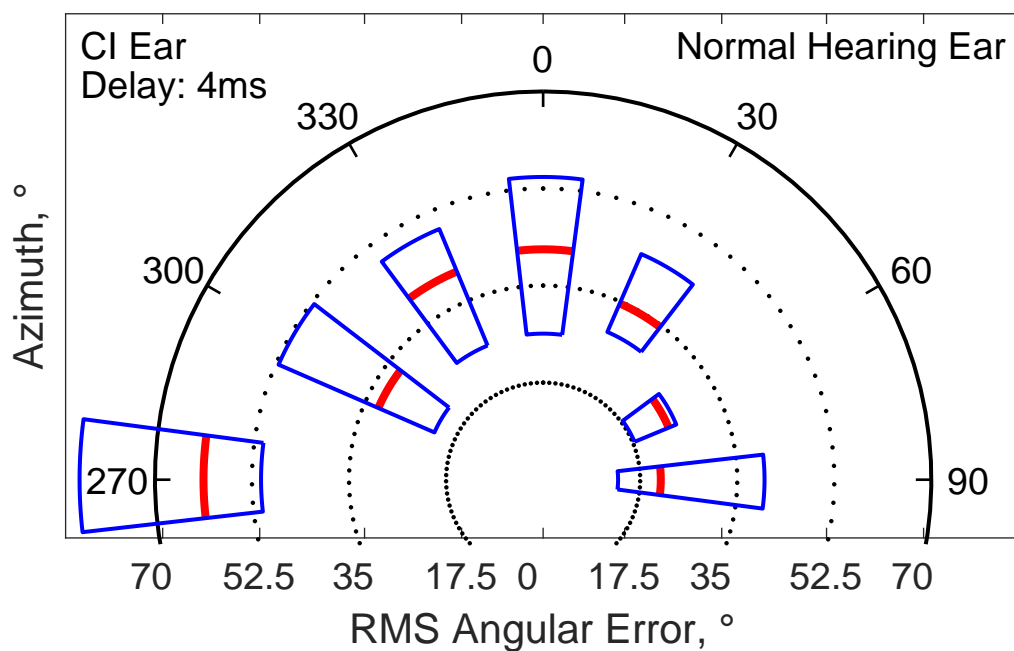
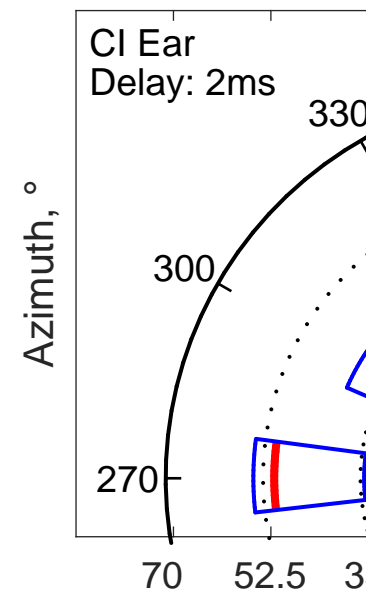
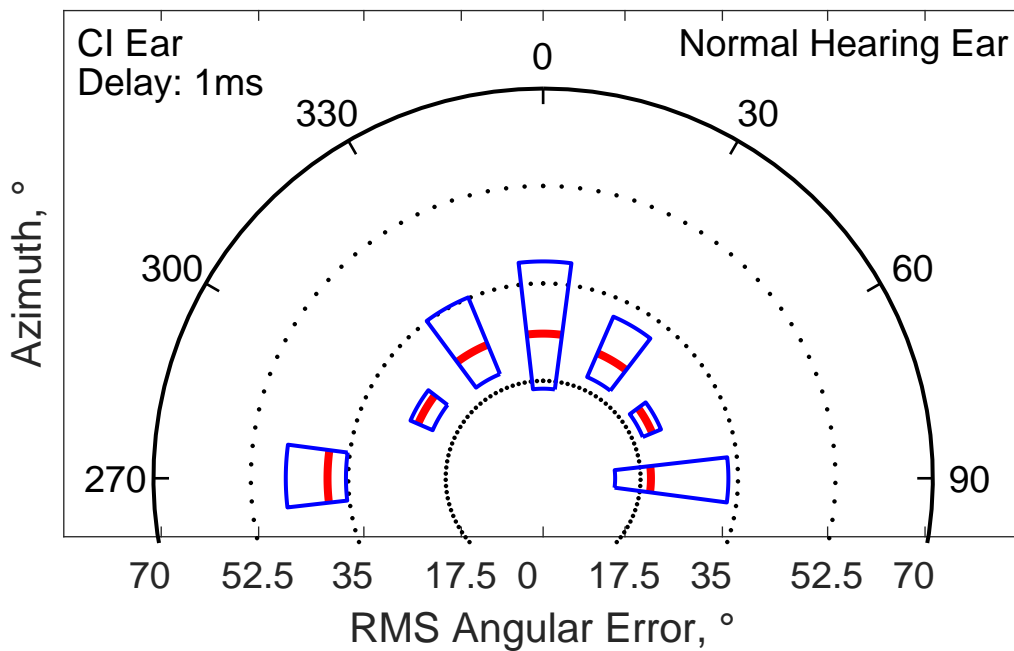
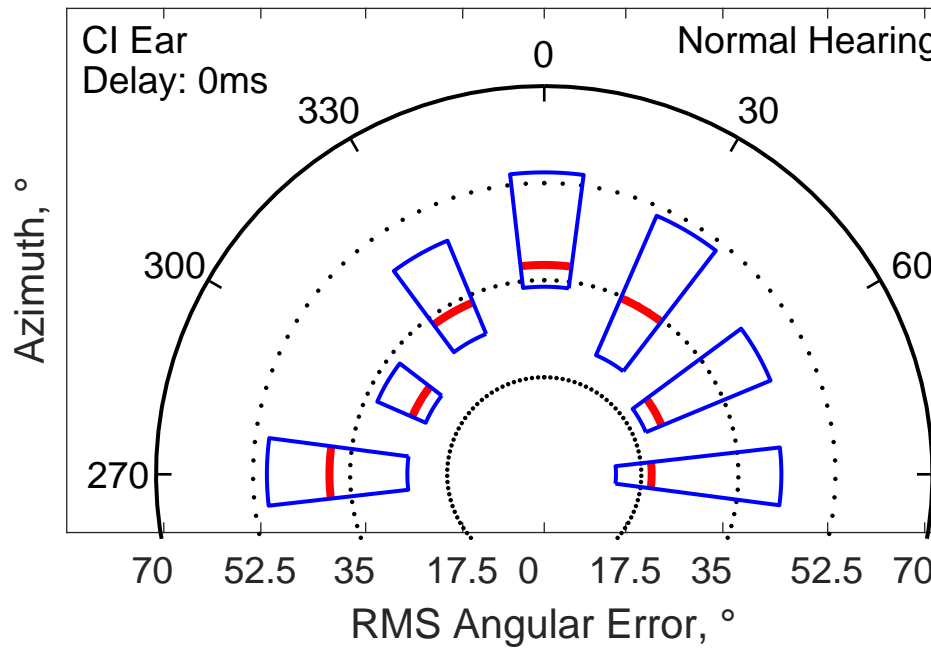
Figure 6: Speech reception thresholds expressed in signal-to-noise ratio for signal delays of 0 milliseconds (standard use), 0.5, 1, 2 and 4 milliseconds. Significant differences between test conditions were not found. More strongly negative values represent better performance.



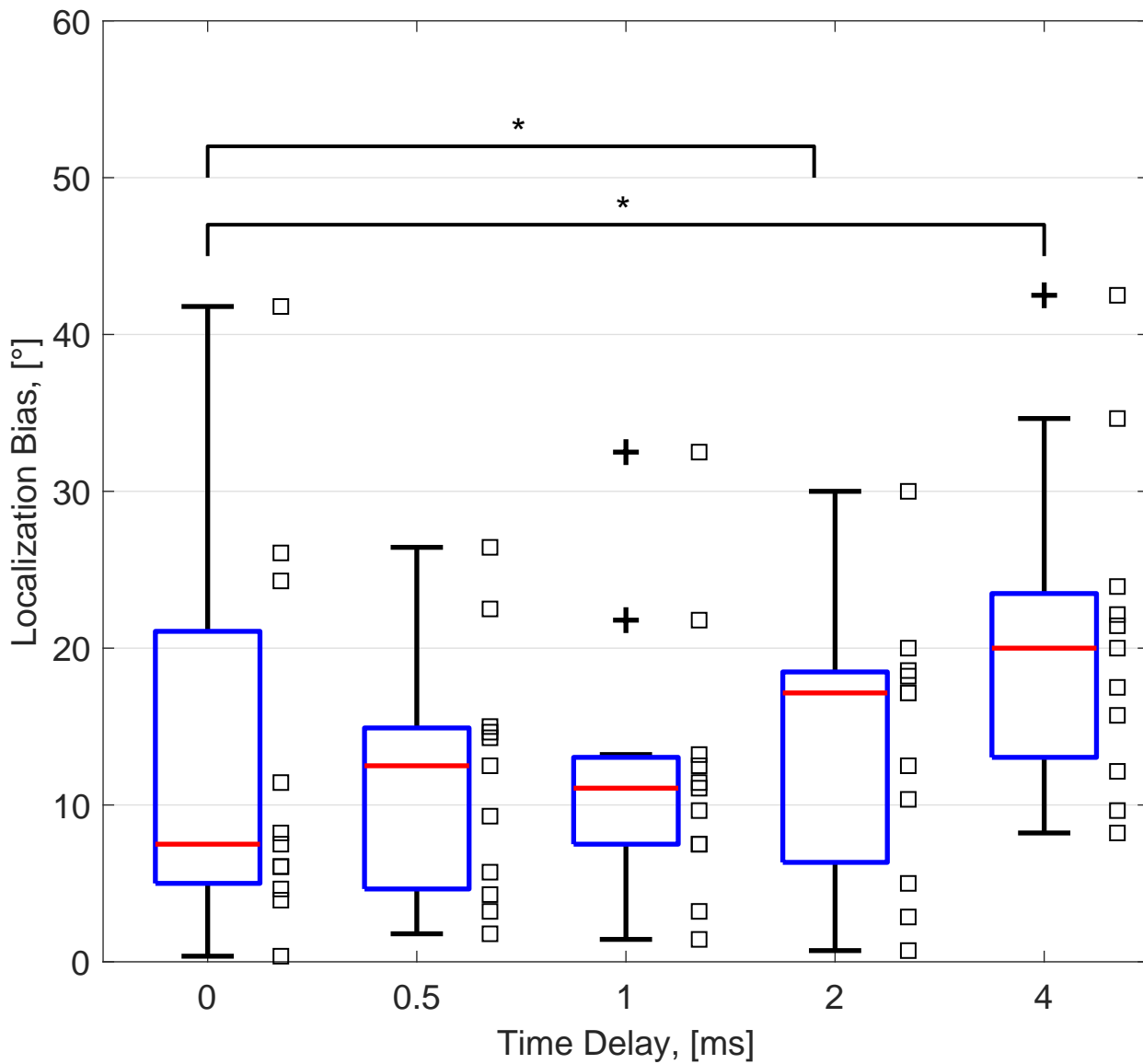


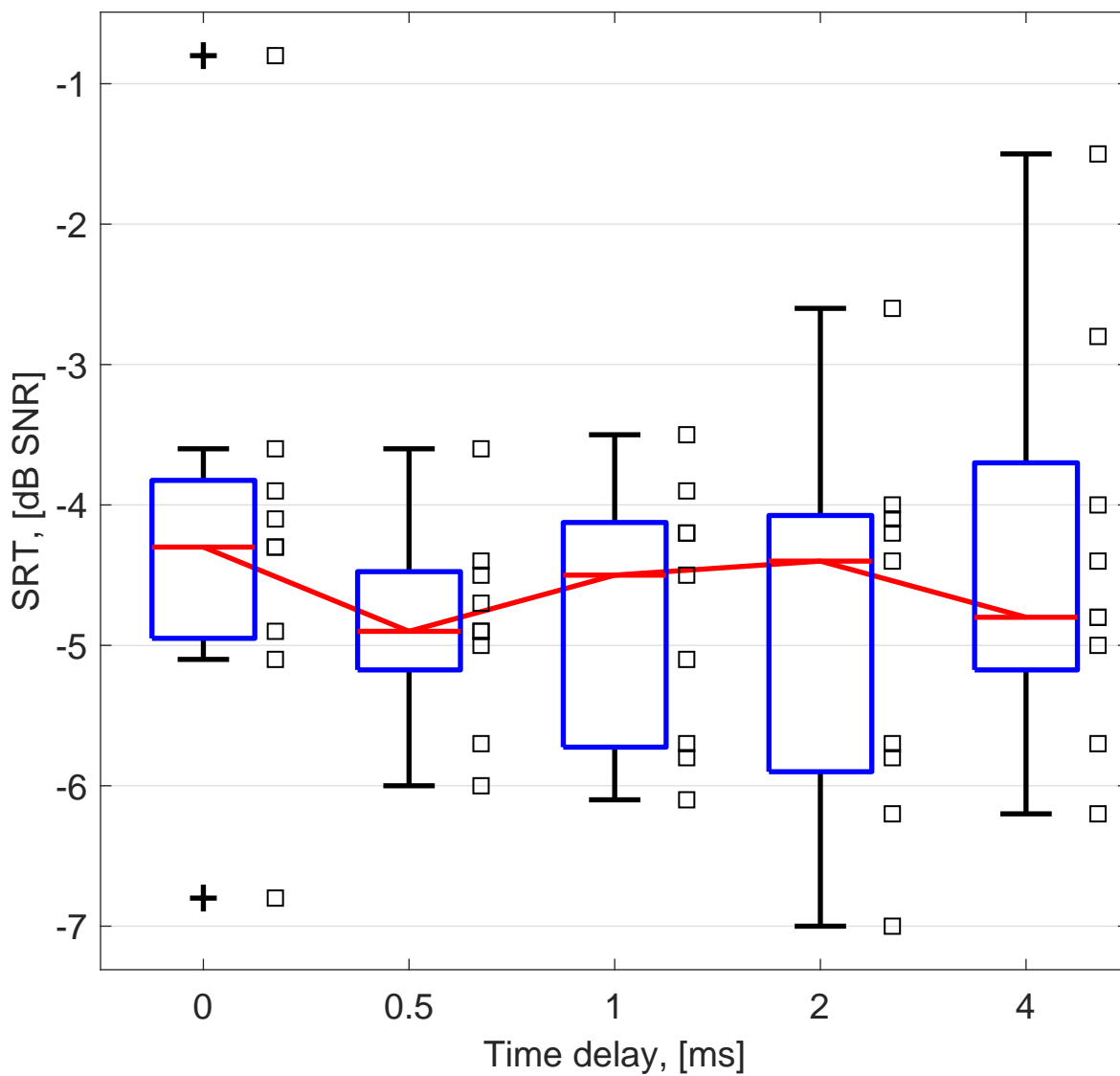
ACCEPTED MANUSCRIPT





MANUSCRIPT





Highlights

of the manuscript “Improved interaural timing of acoustic nerve stimulation affects sound localization in single sided deaf cochlear implant users”

- Compensation of timing differences of cochlear implant systems and normal hearing improves sound localization in patients with single sided deafness
- Signal delays of electrical stimulation in cochlear implants yielding best binaural performance in patients with single sided deafness are in line with latency differences found in auditory brainstem responses
- Synchronization of natural hearing and electrical stimulation via cochlear implant impacts on binaural hearing abilities