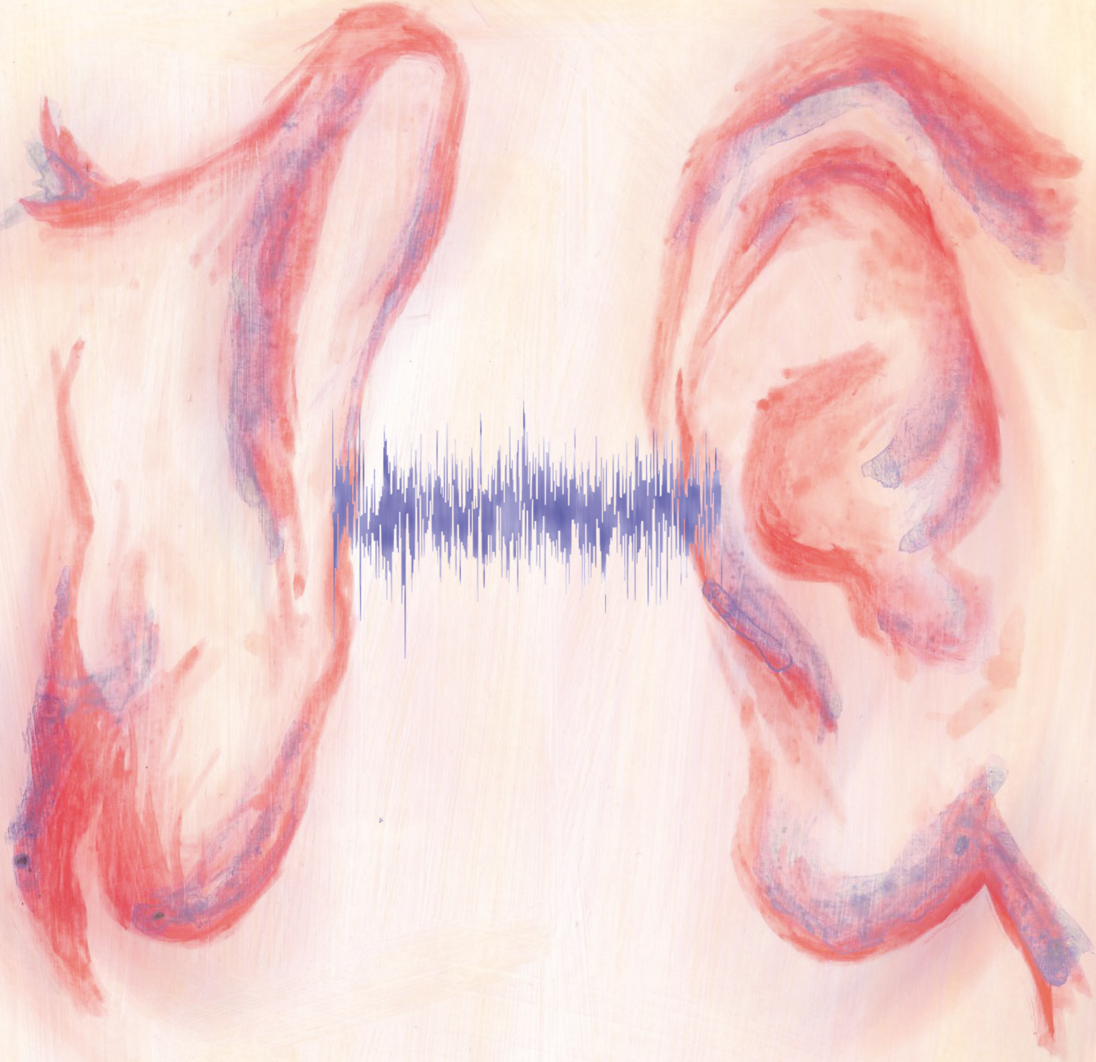
PROGNOSIS IN UNILATERAL AND BILATERAL COCHLEAR IMPLANTATION



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PROGNOSIS IN UNILATERAL AND BILATERAL COCHLEAR IMPLANTATION

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PROGNOSIS IN UNILATERAL AND BILATERAL COCHLEAR IMPLANTATION

Prognose in unilaterale en bilaterale cochleaire implantatie
(met een samenvatting in het Nederlands)

Proefschrift

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aan de Universiteit van Utrecht
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door

Véronique Julie Constance Kraaijenga
geboren op 14 juli 1989 te Geldrop

Promotor:	Prof. dr. R.J. Stokroos
Copromotoren:	Dr. G.A. van Zanten
	Dr. A.L. Smit

Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less. *Marie Curie*

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Chapter 1

Introduction and outline of thesis

GENERAL INTRODUCTION

Physiology of hearing

Hearing is the perception of sound. The ear consists of three compartments: the outer ear, the middle ear, and the inner ear (Figure 1). The outer ear consists of the pinna and the external auditory canal. The middle ear consists of the tympanic membrane and the ossicular chain (malleus, incus and stapes). The inner ear consists of the cochlea, the vestibule and the auditory nerve. The cochlea is a snail-shaped structure with 2 ¾ turns. Inside the cochlea is the organ of Corti. Uncoiled, the cochlea forms a 35 mm long tube. The cochlea consists of three compartments containing fluid: the scala tympani and scala vestibuli contain perilymph and are located on the outside of the cochlea whereas the scala media contains endolymph and is located in the middle. The basilar membrane divides the scala media from the scala tympani and houses the organ of Corti. The organ of Corti is a highly specialized structure containing hair cells: a single row of inner hair cells and three rows of outer hair cells. The human ear contains approximately 3000 inner hair cells and 12000 outer hair cells. The inner hair cells are the actual sensory receptors and are connected to 95% of the afferent nerve fibers which transduce auditory information from the cochlea to the central nervous system. The outer hair cells are connected to the remaining 5% of the afferent nerve fibers.[1,2]

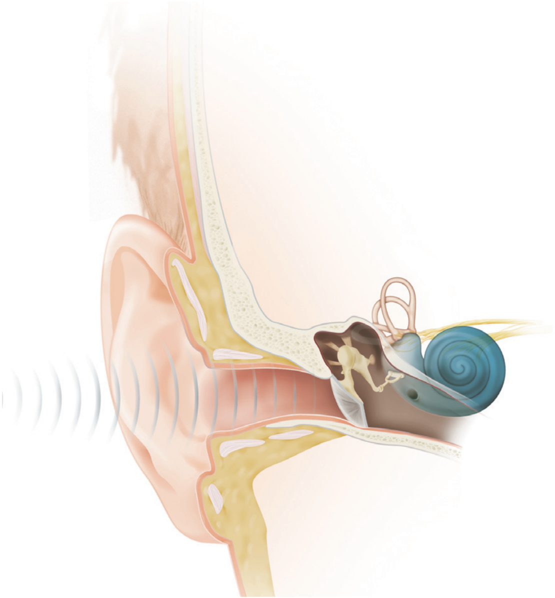

Figure 1 | Anatomy of the human ear. Image derived from: Kraaijenga VJ, Venekamp R, Grolman W. Het cochleair implantaat. Huisarts en Wetenschap. 2016;59(6):260-264.

In normal hearing, sound waves are picked up by the pinna and transmitted through the external auditory canal to the tympanic membrane. The vibrations that are produced by the tympanic membrane are transduced along the ossicular chain to the oval window. The oval window communicates with the cochlea which is in continuity with the vestibule and filled with perilymph. The vibrations induce movement of the perilymph in the cochlea which is transmitted to the basal membrane in the organ of Corti (Figure 2). In the organ of Corti the perilymph movement is converted into action potentials by the inner hair cells which are each innervated by 10-20 peripheral nerve fibers of the spiral ganglion cells. Central axons of the spiral ganglion cells form the vestibulocochlear nerve and terminate in the cochlear nucleus of the brainstem.[3] Subsequently, neurons in the cochlear nucleus send their axons via three main pathways towards the brain: the dorsal acoustic stria, the intermediate acoustic stria and the trapezoid body. The most important pathway is the latter, where the nerve fibers cross the brainstem and innervate the contralateral superior olivary nucleus. Cells within these structures are highly sensitive to time differences and level differences of sounds, therefore, the superior olivary nuclei are of great value in determining sound localization. Axons from the superior olivary nucleus form, together with crossed and uncrossed fibers, the lateral lemniscus which terminates in the inferior colliculus. From there, most axons project to the medial geniculate nucleus of the ipsilateral thalamus, but a few fibers cross to the contralateral side. From the medial geniculate nucleus the primary auditory cortex is innervated in the brain.[3,4]

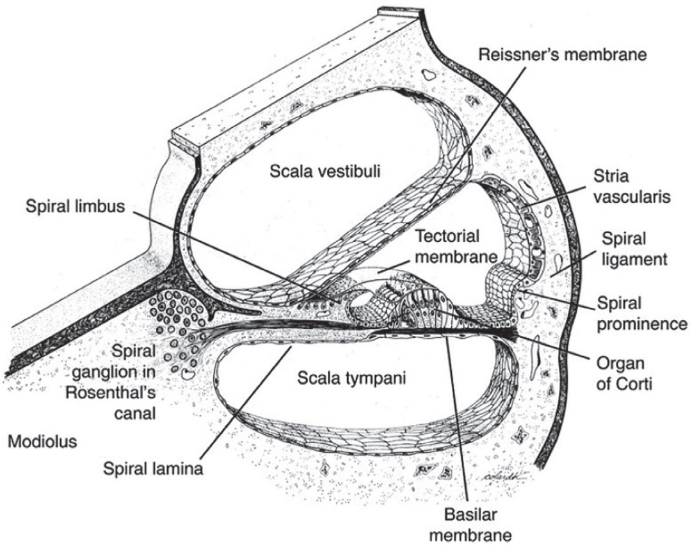

Figure 2 | The organ of Corti (Image derived from Pickles, James O. *Introduction to the Physiology of Hearing*, BRILL, 2012. ProQuest Ebook Central)

The frequency that is perceived by the auditory system depends on the location in the cochlea where the fluid vibrations are converted into action potentials. The cochlea is tonotopically organized, which means each frequency has its own place on the basilar membrane and activates a subpopulation of hair cells and nerve fibers. High frequencies are perceived at the base of the cochlea whereas low frequencies are perceived at the apex of the cochlea. This highly specific tonotopic organization of the cochlea is preserved by the arrangement of the auditory nerve fibers that enter the brainstem in the cochlear nucleus and is maintained throughout the entire auditory pathway. Through this tonotopical organization, we are able to perceive different frequencies.[1]

In addition to perceiving loudness and pitch, a normal hearing person has the extraordinary ability to localize specifically where a sound is coming from as well as focus on speech in competing background noise. The ability to use spatial cues to know where a sound originates from is called spatial hearing. We are able to hear spatially because we use two ears, e.g. binaural hearing. It encompasses not only localization of sound but also the ability to choose a sound source to listen to in an environment with competing sound sources, e.g. sound perception in noise. Binaural hearing is based on three principles: the head shadow effect, the summation effect and the squelch effect.[5,6]

1. Head shadow effect

The head shadow effect occurs in situations with spatially separated speech and competing noise. The head acts a as a physical barrier for sounds. The presence of the head results in a difference in signal-to-noise ratios (SNR) between both ears due to a difference in filtering of sounds (interaural time and level differences). With two functional ears a subject is able to attend to the ear with the most favorable SNR.

2. Summation effect

The binaural summation effect occurs in situations with speech and noise originating from the same location. Binaural summation is the ability of the auditory system to combine input from both ears and to derive benefit from this combined information centrally.

3. Squelch effect

The binaural squelch effect occurs in situations with spatially separated sound and competing noise. The binaural squelch effect is the ability of the auditory system to combine information from both ears centrally and segregate the speech from the noise by using the differences in pitch and loudness of incoming sound between both ears. The noise information in the ear with the poorer SNR is used to improve segregation of speech and noise in the ear with the better SNR. Through the better segregation of speech from noise, speech perception is improved.

Hearing loss

Through deficits of the physiology of hearing we can suffer from hearing loss. This affects 360 million people worldwide, which comes down to 5% of the human population.[7] In the Netherlands, the prevalence of severe hearing loss is 0.74 per 1000 persons.[8] The impact of severe to profound hearing loss or deafness is substantial. Deafness is considered a substantial handicap, which may result in a lack of social assertiveness and lack of interest in the surroundings, which in turn may result in loneliness, depression and decreased participation in society in adults.[2]

Hearing loss is often differentiated in conductive hearing loss and sensorineural hearing loss (SNHL). Conductive hearing loss is caused by decreased sound vibrations in the external ear canal, the tympanic membrane or the ossicular chain in the middle ear. SNHL hearing loss is caused by a decreased amount of functioning hair cells in the organ of Corti in the cochlea or a problem of transmitting the action potentials by the auditory nerve to the auditory cortex. In this thesis we will focus on SNHL and its rehabilitation options. The most common cause of SNHL is pathology in the cochlea, causing a dysfunction of the hair cells in the organ of Corti. Presbyacusis and noise-induced hearing loss are common examples of SNHL. Besides this, hearing loss can be classified according to side (unilateral versus bilateral) and to age of onset. Hearing loss acquired before the development of speech and language skills is called prelingual hearing loss. Hearing loss acquired after the development of speech and language skills is called postlingual hearing loss. In postlingual hearing loss, the auditory pathways from the cochlea to the auditory cortex are already developed whereas in prelingual hearing loss they are not.

The degree of hearing loss is described in a classification of the American Speech-Language- Hearing Association.[9] This classification uses cut-off points in decibels for a subclass of hearing loss. In this thesis, we focus on adult patients with bilateral severe to profound hearing loss, which means an average hearing loss larger than 70 decibel (dB).

Tinnitus

Tinnitus is a common complaint patients seek help for at the otorhinolaryngology department. The prevalence varies largely (between 5% and 49%) based on the patient selection. Since tinnitus is often experienced in conjunction with SNHL, the prevalence of tinnitus is high (66% -86%) in patients with severe to profound hearing loss.[10] The impact of tinnitus may be substantial; symptoms such as sleep deprivation and depression are commonly described. Treatment options are intended to improve coping instead of treating tinnitus.[11] Hearing rehabilitation is known to reduce tinnitus complaints.

Tinnitus is defined as a sound sensation without the actual presence of an external sound source. Typically described forms of tinnitus are buzzing or ringing in the ears. Tinnitus may be divided into subjective and objective tinnitus. Subjective tinnitus is the most common type of tinnitus and entails an experience of sound in the head or ear without an objectified sound source. Objective tinnitus is less common and entails a form of tinnitus where an internal physical sound source is objectified. Tinnitus may have a pulsatile character when the sound source is of vascular origin such as an aneurysm or arteriovenous malformation. Tinnitus may be vibrational or clicking when the sound source is of muscular origin due to a myoclonus for example.[1,12,13] In the remainder of this thesis we will discuss subjective tinnitus only.

Cochlear implantation

When people suffer from hearing loss, hearing rehabilitation can be provided. Hearing rehabilitation is traditionally done with hearing aids. Hearing aids are build-up of a microphone, an amplifier and an element that produces sound. Hearing aids can therefore amplify sounds which enables patients to hear sounds they were no longer able to hear. When SNHL progresses to a severe to profound degree and hearing aids are of limited benefit, a cochlear implant may be considered to rehabilitate hearing abilities. A cochlear implant (CI) system exists of an external part comprising a speech processor with a built-in microphone and a transmitting coil and an internal part containing the receiver and the multichannel electrode array. Sound is picked up by the microphone in the speech processor, and is encoded to a digital signal which is transmitted by the transmitter coil. This coil transmits the digital signal through the skin to the subcutaneous receiver. From the subcutaneous receiver, the signal is transmitted to the surgically placed electrode array in the cochlea. The electrode array is build-up of a bundle of thin contacts. The speech processor divides incoming sound into different frequencies and subsequently activates different contacts of the electrode array which are coupled to the corresponding frequencies in the cochlea resulting in depolarization of specific neuronal populations within the cochlea. Since the CI is able to use the tonotopic organization of the cochlea, stimulation of different contacts within the electrode array results in the perception of different pitches (Figure X).

In 1961 the first CI was implanted by Doctor Williams House and Doctor John Doyle in Los Angeles, California. In 1972 the Food and Drug Administration approved cochlear implantation in postlingually deafened adults with SNHL using the House 3M single electrode system. In 1985 the first cochlear implantation with a House 3M implant was implanted in the University Medical Center of Utrecht. Even though this CI only contained one electrode in its array, patients were able to perceive sounds. With the introduction of multichannel electrodes, performance with a CI rapidly improved enabling CI users to understand speech in quiet.

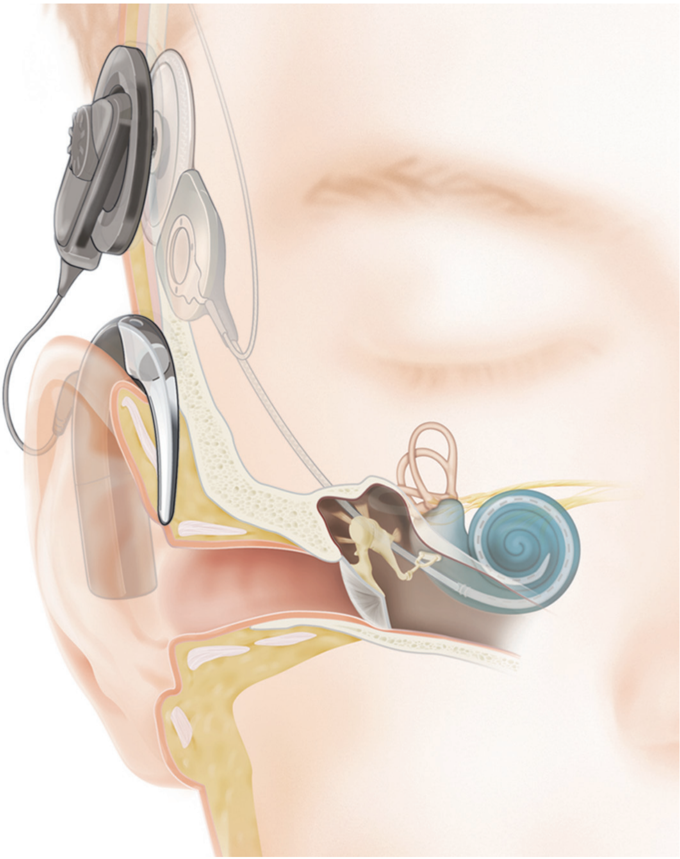

Figure 3 | Hearing with a cochlear implant. Image derived from: Kraaijenga VJ, Venekamp R, Grolman W. Het cochleair implantaat. Huisarts en Wetenschap. 2016;59(6):260-264.

Unilateral cochlear implantation

An abundance of literature shows that cochlear implantation is the preferred treatment for children and adults with severe to profound hearing loss when conventional hearing aids are no longer effective.[14–16] CI candidacy has changed largely over the years. Originally, a CI was solely provided to patients with postlingually acquired bilateral severe to profound SNHL. Nowadays, indications have broadened to patients with prelingual hearing loss, patients with residual hearing and even to patients with unilateral hearing loss depending on national reimbursement criteria.

Although speech perception scores in quiet are fairly good for most CI recipients, not everyone benefits equally from their implants.[17–19] Especially early implanted children and adults with late onset deafness can obtain high levels of speech perception, with star performers who can even appreciate musical compositions.[3] Adults who were deafened at childhood and implanted with a CI in adulthood are known to be rather poor performers.[20–22] Nonetheless, performance with a cochlear implant is difficult to predict before implantation. The ability to predict performance before implantation would enable clinicians to improve preoperative counselling. In 2014 a retrospective cohort study was performed in the University Medical Center of Utrecht in order to predict post-implant speech perception outcomes based on pre-implant patient characteristics with the ultimate goal to improve pre-implant counselling.

Bilateral cochlear implantation

Evidence from several observational studies has shown that bilateral cochlear implantation (BiCI) is beneficial for patients in order to gain spatial hearing and localization abilities.[23–26] These benefits have led to an international consensus to implant children with bilateral CIs. Since 2012, Dutch health care insurance companies reimburse bilateral CIs in children up to 5 years of age who have a hearing loss of more than 60 dB at the frequencies 2kHz and 4kHz with conventional hearing aids.[27,28] There is an ongoing discussion in the Netherlands on whether or not BiCI should be provided and reimbursed as standard care for adults, as it is in Germany and Scandinavia for example. In 2006, the *College voor Zorgverzekeringen* nowadays called *het Zorginstituut Nederland* ruled in favor of reimbursing BiCI only in adults who are deafened by meningitis because of the risk of ossification of the cochlea, which diminishes the chances of a successful implantation later in life.[27] The lack of international consensus on reimbursement of BiCI in adults is also evident in the United States, where reimbursement of bilateral Cis is highly dependent on the way a person is insured, e.g. employer-based or government-based.[29] Recently, a questionnaire was sent to adult CI recipients in the United States of which only 50% responded to be bilateral CI users.[30] Up till now, observational BiCI studies have focused on the difference between BiCI and UCI. Most of these studies followed patients up for a relatively short time.[23–26] Furthermore, in these studies the BiCI population comprised of either simultaneously implanted patients, sequentially implanted patients or a mixture of both.[23–26] Little is known about the difference in results between simultaneous BiCI (simBiCI), implanting both implants in one surgery, and sequential BiCI (seqBiCI), implanting two implants in two staged surgery.

AIMS OF THIS THESIS

The aims of this thesis are threefold. First, we aim to predict cochlear implantation outcomes based on pre-implant factors in order to improve patient counseling preoperatively as well as optimize inclusion criteria. Second, we aim to add scientific proof to the existing literature on the long-term benefit of BiCI over unilateral cochlear implantation (UCI) in adult patients with severe to profound hearing loss. Third, we aim to compare hearing results after simBiCI versus seqBiCI in bilateral cochlear implant recipients.

OUTLINE OF THIS THESIS

This thesis consists of two parts. The first part focuses on predicting post-implant speech perception outcomes based on pre-implant patient and implantation characteristics.

Chapter 2 describes the results of a retrospective cohort study performed in the University Medical Center Utrecht evaluating the association between pre-implant characteristics and post-implant speech perception performance in adults with bilateral severe to profound hearing loss who received a single CI. **Chapter 3** presents the results of a systematic review on the effect of side of implantation on post-implant performance in adults and children with severe to profound hearing loss after UCI.

The second part of this thesis focuses on evaluating the difference in results between BiCI and UCI as well as the differences in results between simBiCI and seqBiCI. In order to do so, our research group started a multicenter randomized controlled trial (RCT) in 2009 to evaluate the effectiveness of BiCI in adult patients with bilateral severe to profound hearing loss. Thirty-eight participants were randomly allocated to a simBiCI group or a seqBiCI group between 2010 and 2012. Participants in the simBiCI group received two CIs in one surgery whereas the participants in the seqBiCI group received two CIs sequentially with an inter-implant interval of 2 years. Follow-up was annually during four years to assess outcome. The study design allowed us to compare the difference in results between simBiCI versus seqBiCI additionally. All data used in this part of the thesis were collected as part of this RCT. **Chapter 4** describes the three year results of this RCT comparing simBiCI versus seqBiCI in a between-subjects design and UCI versus seqBiCI in a within-subjects design. In **Chapter 5**, the ability to make use of the squelch effect was evaluated in our group of patients who received two CIs simultaneously during three years of follow-up. In **Chapter 6**, the ability to make use of the squelch effect was evaluated in our group of patients who received their CIs sequentially during a median of four years of follow-up. In **Chapter 7** we present the long-term (four years) observational and self-reported outcomes of the RCT using longitudinal data analyses. In addition, complications that occurred during the RCT are described. In **Chapter 8** a general discussion of the preceding chapters is presented.

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PART 1

Unilateral cochlear implantation

Chapter 2

Factors that influence outcomes in cochlear implantation in adults, based on patient-related characteristics: A retrospective study

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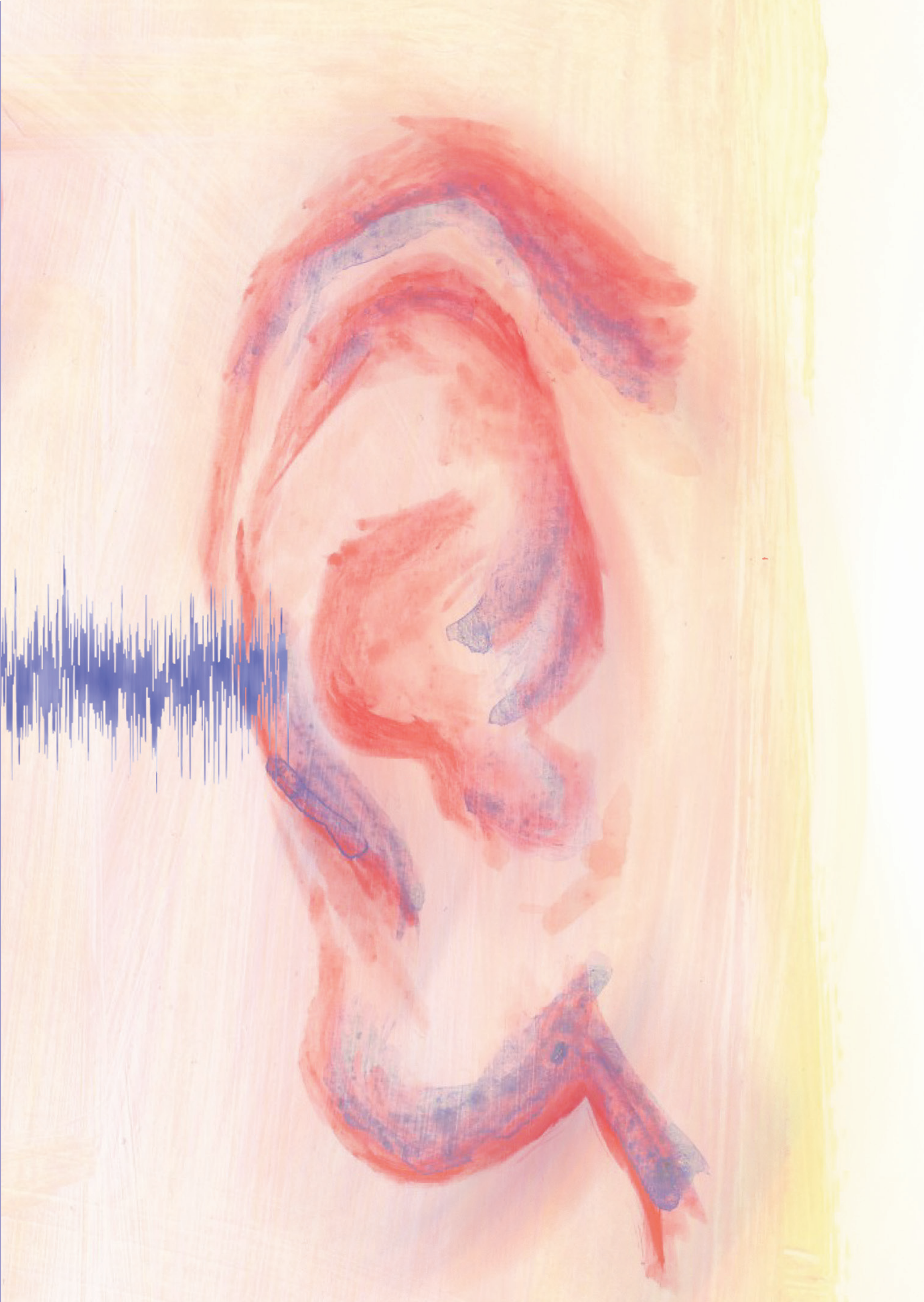
Clin Otolaryngol. 2016;41(5):585-92.



ABSTRACT

Objective: Outcomes in speech perception following cochlear implantation in adults vary widely. Many studies have been carried out to identify and quantify factors that influence outcomes. This study adds a new dimension to pre-existing literature.

Design: Single-center retrospective cohort study.

Setting: University Medical Center Utrecht, the Netherlands.

Participants: A total of 428 adults with bilateral severe-to-profound sensorineural hearing loss unilaterally implanted between February 1988 and March 2014.

Main outcome measures: Univariable and multivariable linear regression analyses were carried out to identify factors that may influence outcome after cochlear implantation. Consonant-vowel-consonant word scores were recorded pre- and post-implant and were used as outcome measure in two groups of patients (prelingually and postlingually deafened adults). As an added dimension, multiple imputation was implemented and evaluated to tackle 4% (17/407) missing data.

Results: For postlinguals, pre-implant speech perception score and age at onset of deafness are positive predictors and meningitis and otosclerosis as cause of deafness are negative predictors of post-implant speech perception. This model accounted for 26% of variance. For prelinguals, pre-implant speech perception score is the only strong positive predictor (b 0.524; $P < 0.001$). This model accounted for 31% of variance. Age at implantation was not a significant predictor in either group.

Conclusions: Speech perception is predicted by pre-implant speech perception, age at onset of deafness and etiology (meningitis and otosclerosis) for postlinguals and solely pre-implant speech perception for prelinguals. Age at implantation is of lesser importance in predicting speech perception outcome post-implant. Multiple imputation is a useful statistical technique when analyzing incomplete data sets.

Key words Cochlear implant – Hearing loss – Patient characteristics – Predictive model – Adult – Speech perception – CI performance – Personalized Cochlear Implantation Care – Prelingual – Postlingual

Level of evidence 2b

INTRODUCTION

Cochlear implantation is a common treatment for bilateral sensorineural hearing loss (SNHL) in patients who cease to benefit from hearing aids. To determine which patients benefit most from a cochlear implant (CI), multiple studies have evaluated post-implant CI performance with pre-implant patient demographics.[1–15] Literature has consistently shown great differences in outcome between prelingually and postlingually deafened patients.[16–18] Due to large amounts of unknown etiologies in previous studies, a clear pattern has not yet emerged between etiology of deafness and post-implant performance.[1,2,12,13] Duration of deafness, or derived factors such as percentage of life deaf or age at onset of deafness, has shown a consistent correlation with post-implant outcome, as well as pre-implant speech perception tests.[1,2,5,9,11,13,15] Contradictory results have been reported about the effect of an advanced age on speech perception performance.[2,4,6,9,10,12,13,15]

A problem seen in all previous studies, is the large amount of missing data.[2,3,5,9,10] For handling missing data, all these studies used a complete case analysis, which is simply deleting participants with missing data. Because missing data are seldom missing completely at random, complete case analysis leaves a non-random subset of the original study sample, yielding an invalid predictive performance. Multiple imputation is a generally preferred method for handling missing data in prediction research.[19] In this strategy, missing observations are substituted by plausible estimated values derived from analysis of the available data.[19] This study describes a single-center cohort study with a small proportion of missing data which was handled by multiple imputation.

As mentioned, literature of the past decades has shown contradictory results of pre-implant predictors of post-implant speech perception. A better understanding of these factors could aid clinicians in patient selection and counselling of patients' expectations. Ideally, individual outcome of cochlear implantation should be predicted after a patient's completion of the multidisciplinary assessment, based on their medical history and audiological tests. Therefore, the aim of our study was to assess the predictive value of patient characteristics for post-implant speech perception.

MATERIAL AND METHODS

Ethical considerations

The study was performed in accordance with the Declaration of Helsinki. Considering the retrospective design and use of anonymized data, exemption for full review from the Local Medical Ethics Committee was obtained (WAG/th/14/037231).

Design and study population

A retrospective chart review was performed of adult patients with bilateral severe-to-profound SNHL who underwent unilateral cochlear implantation in the University Medical Center Utrecht from February 1988 to March 2014. Severe-to-profound hearing loss was defined as a mean pure-tone average (PTA) ≥ 70 dB HL, in this article called 'deaf'. The PTA was calculated by averaging the unaided pure-tone air-conduction thresholds at ½, 1, 2, 4 kHz. To predict any patients' post-implant speech perception, pre- and postlingually deafened patients were both included in this study but analyzed independently. A patient was classified prelingually or postlingually deaf when deafness occurred <1 year old and >4 years old, respectively.[20] When deafness occurred between 1 and 4 years or in case of doubt, patient charts were reviewed and lingual status was determined by education (for the deaf or regular education) and expert deliberation. Etiology of deafness was divided into groups, of which an equal course of disease and outcome was estimated.

CI performance

Speech perception tests were performed at 65 dB SPL in sound-treated booths. Speech material consisted of open-set Dutch words of consonant-vowel-consonant (CVC) structure and the percentage of correctly repeated phonemes was scored.21 In case the CVC word test was carried out solely audio-visually or visually because patients were unable to understand speech without visual clues, the audiological CVC word score was set at 0%. Non-user, revision or reimplantation, explantation and death were considered endpoints of the study.

Data analysis

Statistical analysis was performed with IBM SPSS Statistics, version 21. Randomly missing data in CVC scores were handled using multiple imputation. This statistical method created five separate databases with estimated scores dependent from related parameters based on a random draw from different estimated underlying distributions. Subsequently, a pooled database with imputed CVC scores for randomly missing data was created providing a superior estimation of the outcome compared to complete case analysis.[19,22] As a sensitivity analysis, the original data were also analyzed for comparison, in which all cases with missing data were eliminated. Another sensitivity analysis was performed using only patients with full insertions. The data were not normally distributed. The Wilcoxon signed rank test and the Mann–Whitney U test were used for comparisons. Pearson correlations were used for regression analyses, in the assumption of the applicability of the central limit theorem in large amounts of nonparametric data.[23] Medians and ranges were used to display data. Univariable linear regression analyses were performed to determine the predictive value of individual variables. The predictive value was stated by standardized regression coefficients (*b*) accompanied by *P* values and standard deviations. Selection of predictors for multivariable regression analysis was based on hierarchically relevant predictors. Multivariable regression analysis was carried out using a backward method. The model's accuracy was expressed by the R square, the explained variance of the model. Categorical variables were transformed into dummy variables and entered in the regression simultaneously. Progressive SNHL was used as the reference etiology, for this was the largest category (42%) and is considered homogeneous.

RESULTS

Description of cohort

A total of 428 adult patients who received a multichannel CI were included. The majority of implantees acquired SNHL postlingually (86% n = 370) versus 14% (n = 58) prelingually. The median age of implantation was 41 years (range 18–65) for prelinguals and 55 years (range 18–89) for postlinguals. The pre-implant median PTA was 115 dB (range 73–130 dB) in both ears. The implanted ear had a higher mean PTA (116 dB) than the contralateral ear (114 dB) ($P < 0.001$). The median duration of deafness of the implanted ear was 40 years (range 18–65) for prelinguals and 10 years (range 0–76) for postlinguals. This was equal for the contralateral ear; 40 (range 18–65) for prelinguals and 9 years (range 0–85) for postlinguals. The median age at onset was 0 years (range 0–3) for prelinguals and 41 years (0–84) for postlinguals (Tables 1 and 2).

Table 1 | Baseline characteristics of prelinguals (N=58)

Biographic data	**Median***	**Range**
Age at implantation	41	18-65
Age at onset of deafness	0	0-3
Duration deafness CI ear	40	18-65
Duration deafness other ear	40	18-65
Preoperative non-aided CVC score (%) (n=24)	0	0-1
Preoperative best aided CVC score (%) (n=44)	9	0-73
Preoperative PTA both ears (dB)	113	86-130
Follow up	5.6	1.3-15
Etiology	**n**	**%**
Congenital	44	76
- e causa ignota	26	
- intrauterine infection	9	

Table 1 | Continued

Biographic data	**Median***	**Range**
Congenital	44	76
- perinatal events	8	
- usher	1	
Labyrinth malformation	1	1.7
Meningitis	8	14
Infectious	2	3.4
Progressive	3	5.2
Male:female ratio	19:39	33:67

*Reported in years unless otherwise noted

Table 2 | Baseline characteristics of postlinguals (N=370)

Biographic data	**Median***	**Range**
Age at implantation	56	18-89
Age at onset of deafness	41	0-84
Duration deafness CI ear	10	0-76
Duration deafness other ear	9	0-85
Preoperative non-aided CVC score (%) (n=191)	1	0-18
Preoperative best aided CVC score (%) (n=355)	11	0-88
Preoperative PTA both ears (dB) (mean)	115	73-130
Follow up	10.2	1,2-27
Etiology	**n**	**%**
Progressive	178	48.1
Congenital	32	8.6
Meningitis	52	14.1
Infectious	34	9.2
Trauma	19	5.1
Otosclerosis	21	5.7
Sudden deafness	18	4.9
Meniere’s disease	11	3.0
Iatrogenic	3	0.8
Labyrinth malformation	2	0.5
Male:female ratio	174:196	47:53

*Reported in years unless otherwise noted

Cochlear implantation

The majority of the implants were from Cochlear (59%), followed by MedEl (32%) and a small proportion from Advanced Bionics (8%). Patients were implanted in the left ear in 50%. In three patients, a previous attempt at implantation failed due to obliteration of the cochlea by meningitis (n = 2) and otosclerosis (n = 1). Full insertion was achieved in 93% of patients. In 28 patients, the electrode was inserted partially (ranging from 25 to 94%) of which 32% were meningitis and 7% were otosclerosis patients. In three patients, insertion data were missing.

Follow-up

The median follow-up was 9 years (range 1–27). Of the full cohort, 394 patients completed the audiological follow-up. Seven patients had become non-users, and six patients had been explanted before 1 year for the following reasons: pain (n = 2), malfunction (n = 1), pain and malfunction (n = 2) and infection (n = 1). Three implants were revised within 1 year due to malfunction (n = 2) and pain (n = 1). One patient was re-implanted and simultaneously implanted in the contralateral ear because of an incomplete insertion through the internal meatus acousticus due to aplasia of the mastoid and an angled internal acoustic meatus. Four patients died, and 17 patients were lost to follow-up during the first year for the following reasons: no attendance of follow-up meeting (n = 5), sickness (n = 2), transfer to other center (n = 2), unknown (n = 8) (Figure 1).

Pre-implant and post-implant hearing and speech performance data

Pre-implant CVC scores were measured in the best-aided condition with uni- or bilateral hearing aids as well as without amplification. In 20 (5%) cases, the pre-implant CVC score was missing. The median pre-implant CVC score without amplification was 0% (n = 215) of which only two patients scored >1%. For analysis, the median pre-implant best-aided CVC score was used, which was 11% for postlinguals and 9% prelinguals ($P = 0.052$). Median CVC score 1-year post-implant was 58% (range 0–89%) after imputing 4.0% (n = 17) scores that were randomly missing. Prelinguals performed significantly worse than postlinguals (score 26% (0–85) versus 62% (0–95) $P < 0.001$) (Figure 2).

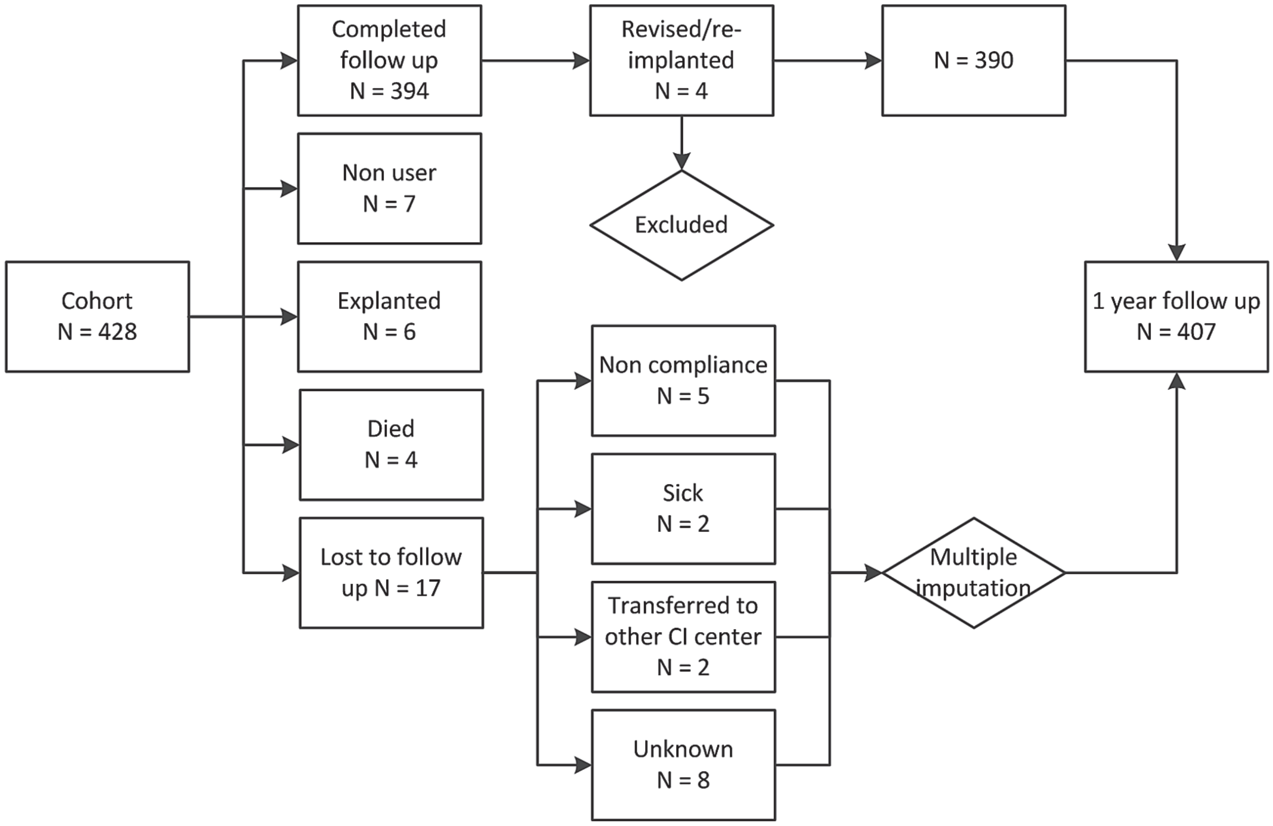


Figure 1 | Flow chart of included patients, lost to follow up and endpoints of study.

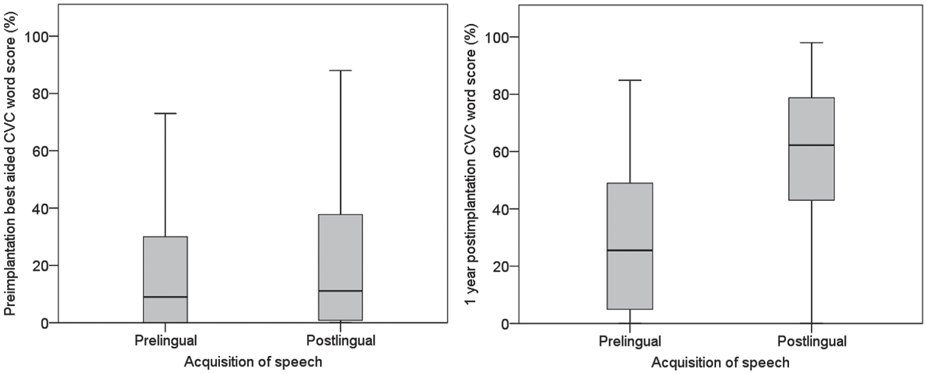


Figure 2 | Preoperative best aided and 1 year postimplantation CVC word scores for prelinguals and postlinguals.

Linear regression analyses

Postlinguals. Table 3 shows the univariable regression analysis for postlinguals. Age at onset of deafness, pre-implant best-aided CVC score and PTA, age at implantation, duration of deafness, etiology and brand were significant associates of post-implant speech perception. We performed multivariable regression analysis using the variables hierarchically proven to be predictive of post-implant speech perception in earlier studies (e.g. age at implantation, age at onset of deafness, etiology, duration of deafness, longest duration of deafness of either ear, pre-implant best-aided CVC score and PTA, gender and choice of ear).[1–6,9,12,13,15] Age at onset of deafness and pre-implant best-aided CVC scores were significant positive predictors ($P = 0.006$ and $P < 0.001$). Meningitis was a significant negative predictor ($P = 0.015$). Otosclerosis was no significant predictor in the multiple imputation data but a significant negative predictor in the original data ($P = 0.008$). Age at implantation was no longer a predictor of outcome as is comprehensible from Figure 3. The predictive value of these factors for post-implant outcome accounted for 26% of variance (Table 4).

Prelinguals. Table 5 shows the univariable regression analysis for prelinguals. Pre-implant CVC scores ($P < 0.001$) and PTAs (CI ear $P < 0.001$ and both ears $P < 0.01$) were positive predictors. Age at implantation, age at onset of deafness, duration of deafness, etiology, pre-implant best-aided CVC score and PTA were selected for inclusion in multivariable regression analysis. Only pre-implant best-aided CVC score remained a predictor (b: 0.50, $P < 0.001$) (Table 6). This explained 31% of the variance. Labyrinth malformation as a predictor was not significant in original data and close to significant in the model after multiple imputation ($P = 0.0507$).

Table 3 | Univariable linear regression analysis – postlingual deafness

Variable		**Original data**			**Multiple imputation**		
		Beta	**P**	**SD**	**Beta**	**SD**	**P**
Age at implantation		.150	.005*	.089	.162	.089	.002**
Age onset deafness		.212	.000***	.064	.218	.063	.000***
Etiology	Progressive eci	Ref					
	Congenital	-.058	.287	4.675	-0.050	4.702	.349
	Meningitis	-.225	.000***	3.805	-0.227	3.806	.000***
	Infectious	-.009	.867	4.493	-0.005	4.676	.934
	Trauma	-.019	.729	6.020	-0.015	6.181	.779
	Otosclerosis	-.067	.219	6.008	-0.068	5.988	.206
	Sudden deafness	-.051	.345	6.358	-0.047	6.519	.386
	Meniere's disease	.098	.069	7.583	0.098	7.743	.068
	Iatrogenic	-.028	.608	14.413	-0.026	14.623	.629
	Labyrinth malformation	.106	.050*	17.534	0.104	17.779	.050
Brand	Cochlear	Ref					
	Advanced Bionics	.125	.021*	5.326	0.119	5.436	.032*
	MedEl	0.085	.118	2.882	.094	2.880	.078
DoD implanted ear		-.135	.012*	.087	-.133	.087	.013*
DoD contralateral ear		-.069	.202	.080	-.070	.080	.195
Longest DoD either ear		-.102	.060	.078	-.099	.080	.068
Preoperative best-aided CVC score (%)		.354	.000***	.053	.344	.054	.000***
Preoperative PTA (dB)		-.354	.000***	.099	-.351	.100	.000***
Preoperative PTA operated ear (dB)		-.300	.000***	.096	-.294	.101	.000***
Preoperative PTA contralateral ear (dB)		-.312	.000***	.080	-.312	.080	.000***
Gender		-.075	.164	2.684	-0.073	2.738	.181
Side		-.009	.867	2.691	-0.014	2.679	.787

Beta: Pearson standardized regression coefficient, SD: standard deviation, dB: decibel, yr: years; ref: reference group, NS: not significant in univariable analysis, *: p<0,05%, **: p<0,01%, ***:p<0,001%

Table 4 | Multivariable linear regression analysis – postlingual deafness

Variable		**Original data**			**Multiple imputation**		
		Beta	**SD**	**P**	**Beta**	**SD**	**P**
Age at implantation		Excl					
Age onset deafness		.218	.064		.000***	.067	.006**
Etiology	Progressive	Ref					
	Congenital	-.022	4.558	.679	-0.058	4.711	.346
	Meningitis	-.124	3.940	.024*	-0.151	4.168	.015*
	Infectious	-.074	4.505	.150	-0.024	4.713	.747
	Trauma	-.020	5.346	.697	-0.029	5.842	.603
	Otosclerosis	-.132	5.450		.008**	5.593	.061
	Sudden deafness	-.049	6.117		.325	6.729	.237
	Meniere's disease	.086	7.174		.085	7.836	.946
	Iatrogenic	-.042	12.874	.394	-0.067	13.433	.215
	Labyrinth malformation	.060	15.711		0.073	.223	.154
DoD implanted ear		Excl					
Longest DoD either ear		Excl					
Preoperative best-aided CVC score (%)		.347	.053		0.288	.067	.000***
Preoperative PTA (dB)		Excl			Excl		
Gender		Excl			Excl		
Side		Excl			Excl		

Beta: Pearson standardized regression coefficient, SD: standard deviation, dB: decibel, yr: years ; ref: reference group, NS: not significant in univariable analysis, *: p<0,05%, **: p<0,01%, ***:p<0,001%

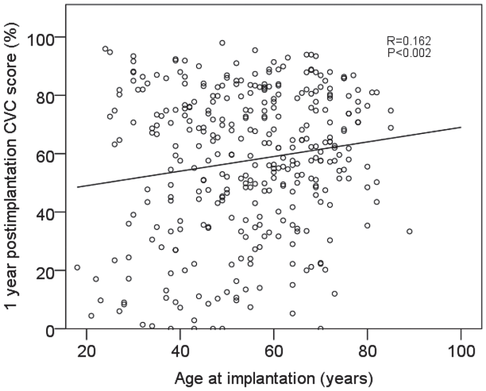


Figure 3 | Correlation between age at implantation and consonant-vowel-consonant word (CVC) scores 1 year postimplantation in a scatterplot.
This scatterplot shows the wide variability in postoperative CVC scores. In univariable regression analysis, age at implantation was a significant predictor of speech perception.

Table 5 | Univariable linear regression analysis – prelingual deafness

Variable		**Original data**			**Multiple imputation**		
		Beta	**P**	**SD**	**Beta**	**SD**	**P**
Age at implantation		-.099	.504	.339	-.076	.324	.593
Age at onset deafness		.068	.648	1.971	.064	1.938	.650
Etiology	Progressive eci	Ref					
	Congenital	-.084	.569	8.479	-0.091	8.299	.529
	Meningitis	-.028	.849	10.710	-0.008	10.337	.958
	Infectious	-.015	.920	18.922	-0.015	18.751	.913
	Labyrinth malformation	-.146	.324	26.194	-0.141	25.931	.312
Brand	Cochlear	Ref					
	Advanced Bionics	-.081	.584	10.113	-0.045	9.810	.757
	MedEl	-.077	.602	7.709	-.102	7.253	.469
DoD implanted ear		-.104	.482	.324	-.006	.281	.967
DoD contralateral ear		-.099	.502	.336	.000	.288	.996
Longest DoD either ear		-.099	.502	.336	.000	.288	.996
Preoperative best-aided CVC score (%)		.512	.000***	.183	.487	.180	.000***
Preoperative PTA (dB)		-.398	.007**	.357	-.363	.330	.007**
Preoperative PTA CI ear (dB)		-.383	.000***	.338	-.334	.312	.012*
Preoperative PTA non-CI ear (dB)		-.333	.021*	.314	-.322	.299	.022*
Gender		-.184	.210	7.884	-0.169	7.820	.253
Side		-.176	.232	7.550	-0.193	7.226	.168

Beta: Pearson standardized regression coefficient, SD: standard deviation dB: decibel, yr: years

Table 6 | Multivariable linear regression analysis - prelingual deafness

Variable	**Original data**			**Multiple imputation**		
	Beta	**P**	**SD**	**Beta**	**SD**	**P**
Age at implantation	NS			NS		
Age onset deafness	NS			NS		
DoD implanted ear	NS			NS		
Preoperative best-aided CVC score (%)	.524	.000***	.187	0.498	.180	.000***
Preoperative PTA (dB)	NS			NS		
Etiology – labyrinth malformation	-.312	.061	28.329	NS		.051

Beta: Pearson standardized regression coefficient, SD: standard deviation, dB: decibel, yr: years

Sensitivity analyses

Complete case analyses showed a median CVC score one year post-implant of 58.6% (range 0–98%). Although the data are comparable, differences in accounted variability and the found predictors are seen (original data set versus multiple imputation dataset). The R square of complete case analysis was 22% for postlinguals and 34% for prelinguals in contrast to 26% and 31% after multiple imputation, respectively. For postlinguals, meningitis reached a higher significance level after imputation ($P = 0.024 \rightarrow P = 0.015$). Otosclerosis was a significant predictor in original data but not after imputation ($P = 0.008 \rightarrow P = 0.061$). Another sensitivity analysis was performed using only patients with full insertions. In this analysis for postlinguals, meningitis and otosclerosis remained significant predictors.

DISCUSSION

Synopsis of key findings

In this study, we aimed to evaluate which pre-implant patient characteristics predict speech perception 1-year post-implant. For postlingual SNHL, pre-implant CVC score, age at onset of deafness, meningitis and otosclerosis as etiology of deafness were identified as statistically significant predictors. For prelinguals, pre-implant speech perception measured in CVC scores was a strong positive predictor for speech perception post-implant.

Postlinguals. In accordance with literature, pre-implant speech perception measured in CVC score has a strong ($b = 0.347$) positive correlation with the height of post-implant CVC scores.[1,7,10] Duration of deafness is calculated from age at implantation minus age at onset of deafness. Due to collinearity between these variables, not all three variables can be predictive of post-implant speech perception in multivariable regression analysis.[2,5,13] In our model, the highest accounted variability was reached with age at onset of deafness as a predictor instead of the more reported duration of deafness in accordance with Leung et al.[8] Friedland et al.[5] and Waltzman et al.[2] found the opposite; however, both studies did not meet the 20:1 ratio for participants and predictors, causing a less reliable model.[24] Age at implantation was not a significant negative predictor in our model, even when duration of deafness and age at onset of deafness were removed from the subset of variables. This contradicts studies that state that diminished speech perception is caused by auditory nerve atrophy.[1,2] Our findings corresponds to recent studies who found no negative correlation between age at implantation and speech perception tests in multivariable analyses.[4,6–8,13] For etiology, we found a significant negative correlation between meningitis and otosclerosis and speech performance scores post-implant. Both etiologies are considered bony disorders as they cause ossification in the inner ear. Our results are in accordance with existing literature that report that cochlear recipients with deafness due to bacterial labyrinthitis perform significantly worse than patients with other etiologies ($P = 0.004$).[2,14] Poorer outcome in otosclerosis patients was established by Rotteveel et al.[25] who found disease progression, occurrence of facial nerve stimulation and fewer electrodes inserted in the cochlea to negatively influence speech perception. Several studies however failed to show a significant correlation between otosclerosis and speech perception. By removing all patients with partial insertions in the sensitivity analysis, we showed that poorer speech perception in patients with meningitis and otosclerosis is not only due to partial insertions but to the disease itself.

Prelinguals. For prelinguals, pre-implant best-aided CVC score was a positive predictor of post-implant speech perception with a regression coefficient of 0.524 ($P < 0.001$) which is in accordance with previous studies.[16,18] Due to collinearity between pre-implant PTA and CVC word scores, pre-implant PTA was no longer a predictor in multivariable regression analysis.

Model comparison with other studies

Over the past two decades, many studies have attempted to identify predictors of speech perception after cochlear implantation, especially for postlinguals. These models were able to account for 9–80% of the post-implant speech perception variance using a variety of predictors in their models and only small amounts of patients.[8–12,14–16,19]

Strengths and limitations

A strength of this study is that this is among one of the largest single-center studies reported. Contrary to earlier studies on predictors for postlinguals, our analysis meets the recommended 20 participants per predictor for continuous outcomes.[24] In addition, our predictors for inclusion in the model were chosen hierarchically instead of the frequently used pre-selection based on univariable significance which carries a great risk of predictor selection bias.[19,24] Furthermore, we used multiple imputation for missing data at random, hereby overcoming the possible bias associated with complete case analysis. By maintaining our sample size, our model was able to find smaller significant predictors such as otosclerosis. As in other studies, a possible limitation to our study is the wide variation in post-implant outcome, ranging from score 0 to 98% in our postlingual cohort, caused large heterogeneity between patients which likely caused the explained variance of 26%. We used multiple imputation to handle our missing data. Using this statistical tool, we were able to maintain our sample size, enlarging statistical power of the study. The possible selection bias associated with complete case analysis is limited through the use of multiple imputation.

CONCLUSION

Predictors of pre- and postlingually deafened patients' speech perception post-implant were investigated for evaluation in the consultation room, which accounted for 26% and 31% of the variance of the outcome, respectively. For postlinguals, pre-implant speech perception score, age at onset of deafness, meningitis and otosclerosis as cause of deafness are predictors of post-implant speech perception. For prelinguals, pre-implant speech perception is a strong positive predictor. Quantification of these predictors may help clinicians predict speech perception after cochlear implantation. This will enable them in estimating personal scores per patient and facilitate personalized cochlear implantation care. Future research in otorhinolaryngology should consider handling missing data by multiple imputation.

Conflict of interest and financial disclosure

Wilko Grolman receives unrestrictive research grants from Cochlear Ltd., Med-El GmbH, Oticon and Advanced Bionics. The authors have no other funding, financial relationships or conflict of interests to disclose.

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Chapter 3

The effect of side of implantation on unilateral cochlear implant performance in patients with prelingual and postlingual sensorineural hearing loss: A systematic review

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ABSTRACT

Objective: Cerebral lateralization of language processing leads to a right ear advantage in normal hearing subjects. The aim of this study was to present a systematic overview of the effect of implantation side on postoperative cochlear implant performance in patients with symmetrical severe-to-profound sensorineural hearing loss.
Data sources: PubMed, Embase and The Cochrane Library databases.
Research methods: Databases were searched from database inception up to January 9th 2017 for cochlear implant and side and all synonyms. Title, abstract and full-text of retrieved articles were screened for eligibility. Then, directness of evidence and risk of bias were assessed. For the included articles, study characteristics and outcome data (hearing and language development) were extracted.
Results: 2541 unique articles were screened, of which twenty were eligible for critical appraisal. No randomized controlled trials were identified. Twelve studies with a high directness of evidence remained for data extraction. Four of six studies including children with prelingual sensorineural hearing loss and four of seven studies investigating adults with postlingual sensorineural hearing loss found a right ear advantage in at least one outcome measurement related to cochlear implant performance.
Conclusion: The available evidence on the effect of side of implantation is of low quality, since study populations and outcome measures are heterogeneous. The majority of studies reveals evidence for a right ear advantage in prelingually deafened children as well as postlingually deafened adults. In view of the present evidence and since no left ear advantage was identified, we cautiously advise implanting the cochlear implant in the right ear when other prognostic factors do not favor the left ear and sensorineural hearing loss is symmetrical.

Key words: Right ear advantage, Right side advantage, Hemispheric dominance, Speech processing, Auditory processing, Speech perception, Cochlear implants, Cochlear implantation, Prelingual deafness, Postlingual deafness, Performance, Lateralization

INTRODUCTION

Since the introduction of cochlear implants (CIs) millions of patients have been implanted, of which the vast majority unilaterally. The selection of ear is based on various functional and anatomical factors, of which duration of deafness and anatomical variations are the most important ones.[1] When sensorineural hearing loss is of equal duration, symmetrical and there are no anatomical constraints, it is argued that a CI should be implanted ipsilateral to a patient's dominant hand for easy device use.[2] The side of implantation could possibly also influence postoperative CI performance.[3] This hypothesis is based on the combination of two assumptions.

The first assumption is that one hemisphere in the brain is of greater influence on brain functions such as speech and language processing compared to the contralateral hemisphere.[4] For speech perception and speech production, left hemisphere dominance is seen in 95-98% of right-handed and in 70-80% of left-handed normal hearing (NH) subjects.[5–7] In contrast, for prosodic language functions such as intonation and accentuation, right hemisphere dominance is seen in the majority of these subjects. Overall, the majority of people have a dominant left hemisphere for speech and language processing.

The second assumption is that although the auditory cortex receives auditory input from both ears, it is most strongly stimulated by the contralateral ear.[8–12] Several functional magnetic resonance imaging studies[11–13] have revealed that auditory input in one ear predominantly projects to the contralateral superior olivary complex and from there to the contralateral auditory cortex. For example, after presentation of monosyllables in a study by Suzuki et al, 2.5 times more voxels were activated in the contralateral auditory cortex compared to the ipsilateral auditory cortex of the stimulated ear.[11]

The combination of the assumptions described above results in a phenomenon called "the right ear advantage" (REA), meaning that in the majority of NH subjects the right ear is most important for the perception and production of speech. Subsequent to a difference in hemispheric lateralization between right-handed and left-handed people, there is a difference in the proportion of people that exhibit a REA between right-handed (79%) and left-handed people (68%).[7,14]

Extensive research in NH subjects has demonstrated that the REA can be influenced by both bottom-up and top-down manipulations.[8,14] For example, in dichotic listening tests, the REA is augmented when the signal intensity in the right ear increases. Conversely, when the signal intensity in the left ear increases, the REA shifts to a left ear advantage. Functional magnetic resonance imaging has demonstrated that the cerebral activation patterns also differ in the "right ear focus" and "left ear focus" situation, indicating the variance in processing of the auditory stimuli. Furthermore, EEG recording of event-related potentials (ERPs) has shown that the ERP latency from the right ear is shorter in the right ear focus situation, while it is longer in the left ear focus situation.[15] These examples demonstrate that the auditory processing and thus the perceived REA is actually affected by top-down manipulations. This led us to question whether hearing loss may affect the REA as well.

Although bilaterally deafened subjects benefit from bilateral CIs more than from a single CI with regards to speech perception in noise and localization of sounds, currently the majority of deaf subjects is still implanted unilaterally mainly due to reimbursement issues.[16] For that reason, it is valuable to know which ear should be implanted when duration of deafness and other factors do not differ between the left and right ear. In that respect it is of interest to investigate whether a REA exists in bilaterally deafened, unilaterally implanted CI users. The aim of this systematic review is to assess the current literature on the effect of side of implantation on postoperative CI performance, in prelingually deafened and postlingually deafened subjects with symmetrical severe-to-profound sensorineural (SNHL).

METHODS

Search and selection

We performed a systematic search in PubMed, Embase and the Cochrane databases on January 9th 2017. The search syntax included relevant synonyms for the search terms 'cochlear implant' and 'side' (please view Table 1 for the search syntax). After removal of duplicates, title and abstract screening was performed independently by two authors (V.J.C.K. and T.C.D.) according to predetermined inclusion and exclusion criteria. Eligible full text articles were retrieved through the databases and by emailing authors. Subsequently, full texts of eligible articles were screened independently (V.J.C.K and T.C.D.). We searched Web of Science for additional relevant articles. Discordances regarding inclusion were resolved by discussion and consensus. The PRISMA statement was used as a guideline for set-up and writing of this systematic review.[17]

Table 1 | Search syntax

Date of search:	09-01-2017
Domain:	Pediatric and adult CI candidates with severe to profound (>90dB) symmetrical SNHL
Determinant:	Unilateral cochlear implantation
Outcome:	Hearing, speech and language development

Database	Search syntax	Hits
PubMed	((((((((cochlear[Title/Abstract]) AND implant*[Title/Abstract])) OR ((cochlear implantation[MeSH Terms]) OR cochlear implants[MeSH Terms])) OR cochlear prosthes*[Title/Abstract]) OR auditory prosthes*[Title/Abstract]) OR auditory implant*[Title/Abstract])) AND ((((((((one-sided[Title/Abstract]) OR one sided[Title/Abstract]) OR single sided[Title/Abstract]) OR left*[Title/Abstract]) OR right*[Title/Abstract]) OR unilateral[Title/Abstract]) OR independent[Title/Abstract]) OR single-sided[Title/Abstract] OR side[Title/Abstract])	1750
Embase	#1: cochlear:ab,ti AND prosthes*:ab,ti #2: cochlear:ab,ti AND implant*:ab,ti #3: auditory:ab,ti AND prosthes*:ab,ti #4: auditory:ab,ti AND implant*:ab,ti #5: ‘cochlea prosthesis’/exp #6: #1 OR #2 OR #3 OR #4 OR #5 #7: ‘one sided’:ab,ti OR unilateral:ab,ti OR independent:ab,ti OR left:ab,ti OR right:ab,ti OR ‘single sided’:ab,ti OR side:ti,ab #8: #6 AND #7	1748
Cochrane	#1: one-sided:ti,ab or “one sided”:ti,ab or “single sided”:ti,ab or left*:ti,ab or right*:ti,ab or unilateral:ti,ab or independent:ti,ab or single-sided:ti,ab or side:ti,ab #2: cochlear:ti,ab and implant*:ti,ab #3: #2 or “cochlear prosthes*”:ti,ab or “auditory prosthes*”:ti,ab or “auditory implant*”:ti,ab #4: #1 and #3	53
Total		3551

Study eligibility criteria

Studies reporting original data on the effect of side of cochlear implantation on postoperative hearing, speech and language outcomes were included. We were interested in unilaterally implanted patients, therefore studies with (some) bilaterally implanted patients were excluded, when no sub analysis for unilateral patients was presented. The outcome measures for cochlear implant performance were clinically administered hearing, speech and language tests.

Quality assessment

As shown in Table 2, we appraised the selected studies independently for directness of evidence (DoE) and risk of bias (RoB), using predefined criteria. DoE was scored by evaluation of population, intervention and outcome. Items were scored as satisfactory, partly satisfactory or unsatisfactory.

Table 2 | Critical appraisal of selected articles

Author (year)	Design	Sample size	Relevance				Validity							
			Patients	Therapy	Outcome	Data extract-ability	Selection bias	Randomization	Blinding	Standardization of outcome	Missing data	Lost to follow up	Follow-up	Confounding
Blamey 2015	RC	1572	●	◐	●	●	●	○	○	●	?	●	○	●
Budenz 2011	RC	108	●	●	●	●	◐	○	○	●	●	●	●	●
Chilosi 2014	CC	20	●	●	●	●	○	○	○	●	●	●	○	●
Deguine 1995	RC	76	●	●	●	○	●	○	○	?	○	○	○	○
Flipsen 2008	CSS	15	●	●	●	●	◐	○	○	●	●	●	○	●
Friedland 2003	RC	58	●	●	●	○	◐	○	○	●	●	●	○	●
Henkin 2008	RC	71	●	●	●	●	●	○	○	●	○	●	○	●
Holden 2012	PC	114	●	●	●	○	◐	○	○	●	?	●	○	●
Kamal 2014	RC	68	●	●	●	●	?	○	○	●	?	●	●	●
Kraaijenga 2015	RC	428	●	●	●	●	○	○	○	●	●	◐	●	●
Mohammed & Sarwat 2014	CSS	50	●	●	●	●	○	○	○	●	?	NA	○	●
Morris 2006	RC	101	●	●	●	●	◐	○	○	●	●	●	○	●
Mosnier 2014	PC	94	●	●	●	●	●	○	○	●	?	?	●	●
Muzaffar & Meyer 2012	RC	84	●	●	●	●	?	○	○	●	●	●	●	○
Roberts 2013	RC	113	●	●	●	●	◐	○	○	●	●	●	○	●
Roman 2004	CCS	7	●	●	○	●	?	○	○	○	●	NA	○	○
Sharpe 2016	RC	96	●	●	●	●	◐	○	○	●	●	●	●	○
Surmelioglu 2014	RC	63	●	●	●	●	●	○	○	●	?	?	●	○

Author (year)	Design	Sample size	Relevance				Validity							
			Patients	Therapy	Outcome	Data extract-ability	Selection bias	Randomization	Blinding	Standardization of outcome	Missing data	Lost to follow up	Follow-up	Confounding
Wang 2011	CSS	177	●	●	●	○	●	○	○	○	?	NA	○	●
Wu 2008	CSS	60	●	◐	●	○	●	○	○	●	●	NA	○	●

Patients	● Patients with bilateral severe to profound SNHL | ○ asymmetrical SNHL
Therapy	● Unilateral cochlear implantation | ◐ Bilateral and unilateral cochlear implantation ○ Bilateral cochlear implantation
Outcome	● Speech perception or speech production test or questionnaire | ○ other tests
Data extractability	● Extractable | ◐ Extractable from figure | ○ Not extractable
Selection bias	● No selection bias | ◐ selective inclusion of non-missing data in retrospective cohort ○ Susceptible to bias
Blinding personnel	● Blinded | ○ No blinding or not mentioned
Standardization of outcome	● Predefined externally validated test | ○ No predefined externally validated test
Missing data	● <10% of missing data or imputed | ◐ 10-20% missing data | ○ >20% missing data ? not reported or unclear
Lost to follow-up	● No lost to follow up | ◐ lost to follow-up, well described | ○ lost to follow-up, not described | NA in cross sectional studies
Follow-up	● At set times measures | ○ different follow up moments
Confounding	● Corrected for or no confounding | ○ confounding present and not corrected for

RC: Retrospective Cohort; PC: Prospective Cohort; CSS: Cross sectional study; CC: Case Control study; NA: not applicable

We assessed RoB by the use of several criteria. First we examined the design of a study and if prospective, whether blinding and randomization were performed. Second, we assessed the standardization of outcome measurements. Standardization was assessed as satisfactory when a validated test was used. Third, we assessed the handling of missing data and loss to follow-up. Fourth, we assessed whether follow-up was at set times or the timing differed per patient. Finally, we assessed handling of possible confounders. Disagreement was resolved by discussion and consensus.

Data extraction and analysis

Two researchers (V.J.C.K. and T.C.D.) independently extracted descriptive data regarding the onset of hearing loss (prelingually or postlingually), side of implantation and hearing, speech and language outcomes from the selected studies.

RESULTS

Search strategy and study selection

As shown in Figure 1, our search identified a total of 3551 articles, of which 2541 were unique. After screening on title and abstract, 30 articles were left for full-text screening. Reference checking yielded five additional possibly relevant articles provided that data could be obtained from the corresponding authors. Two references were published conference abstracts, one was a letter to the editor and twelve articles were not eligible because of a non-corresponding population, intervention or outcome. Consequently, twenty articles were eligible for critical appraisal.

Assessing quality of studies

The critical appraisal is presented in Table 2. No randomized controlled trials (RCTs) were included in the critical appraisal. Two studies were prospective cohort studies[18,19], twelve were retrospective cohort studies[1,2,20–29], five were cross-sectional studies[3,30–33] and one was a case control study.[34]

Two studies included unilaterally and bilaterally implanted patients.[20,33] After contacting the corresponding authors, outcome per side was not extractable in five studies.[18,22,23,32,33] One study investigated electro-physiologically measured syllable discrimination which did not correspond with our predefined inclusion of outcome measures.[3] All of the above resulted in a high DoE in thirteen studies[1,2,19,21,24–31,34] and a low DoE in seven studies.[3,18,20,22,23,32,33]

Blinding and randomization were not performed in any of the studies since no RCTs were identified. Selection of study population was unclear or susceptible to bias in eleven studies.[2,3,18,21,23,25–28,30,31,34] Nine studies had more than 20% missing data or missing data was

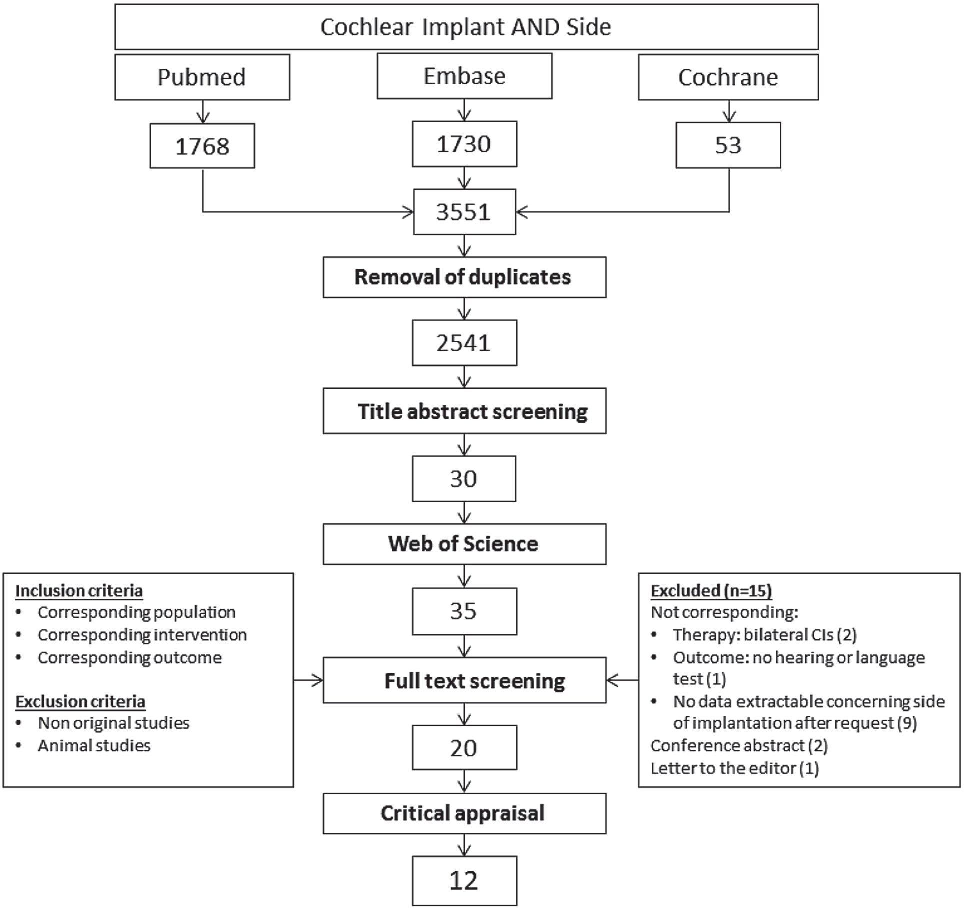

Figure 1. Flow chart of study selection. Search performed on 9 January 2017

unclear. [18–20,22,24,25,29,31,32] In only seven studies patients were equally followed-up at time of testing.[1,19,21,25,26,28,29] All of the above resulted in a low RoB in two studies[1,21], moderate RoB in fourteen studies[2,18–20,23–30,33,34], and a high RoB in four studies.[3,22,31,32] One study was described twice, once in a scientific poster[26] and later on in an article[28], consequently, the poster was excluded from this review.

Finally, twelve studies of which eleven with a high DoE and low or moderate RoB and one study with a high RoB remained for data extraction.[1,2,19,21,24,25,27–31,34]

Data extraction

We were unable to pool data, because there was large clinical heterogeneity among these studies and measures of uncertainty were often not reported. Therefore, we provided a descriptive analysis.

Study characteristics

Most of the studies were retrospective cohort studies, one prospective cohort study,[19] two cross-sectional studies[30,31] and one case-control study.[34] Six studies analyzed children with prelingual SNHL.[24,25,29–31,34] Eight studies examined the effect of side of implantation in adults with postlingual SNHL.[1,2,19,21,25,27,28,31] Two studies reported data on adults with prelingual SNHL.[1,31] One study also included some adolescent implantees with postlingual SNHL.[31] The majority of studies measured speech perception[1,2,19,21,24,25,27–29] whereas three studies measured speech production[30,31,34] with various tests. The study populations varied from 20[34] to 428 patients.[1]

Study outcome: REA

Children

Table 3 contains descriptions of outcome measures used in the included studies. Of the 6 studies investigating the effect of side of implantation in children,[24,25,29–31,34] five included children with prelingual SNHL, whereas Flipsen et al. included children with prelingual and postlingual SNHL. As shown in Table 4, three out of five studies describing prelingual children with SNHL showed a significant REA for speech perception or speech production.[24,25,31] Besides these studies, Flipsen et al. found a significant benefit in the right ear implanted children regarding phoneme intelligibility and accuracy, but not regarding conversational speech perception.[30] Two studies, Chilosi et al. and Surmelioglu et al., did not find a REA.[29,34]

Adults

As shown in Table 5, of the eight studies investigating the REA in adults with postlingual SNHL, four studies reported a significant REA for speech perception[19,21,25,28] and one for

Table 3 | Legend of speech perception tests

Outcome measure	Range	Test content
Speech perception		
CVC/CNC[1,25,27,28]	0-100%	Consonant-vowel/noun-consonant speech perception. Scores can be calculated for the whole word or per phoneme.
CUNY[1,20]	0-100%	City University of New York speech perception test. This test can be administered in quiet and in noise.
HINT[1,28]	0-100%	Hearing in Noise speech perception test.
4 Choice Spondee[24]	0-100%	Closed-set spondee recognition test
High context sentence[24]	0-100%	High context sentence perception test: closed set with open end
AB monosyllabic word[23]	0-100%	Arthur Boothroyd monosyllabic word perception test; prerecorded Hebrew version
AB phonemes[23]	0-100%	Arthur Boothroyd phoneme perception test; prerecorded Hebrew version
Monosyllabic words [24]	0-100%	Open set monosyllabic identification test: within vocabulary of 3-yr old child
Minimal pairs[24]	0-100%	Closed-set speech perception test with 50% chance correct
WIPI[24]	0-100%	Word Intelligibility by Picture Identification: closed-set
LIP[29]	0-16	Listening Progress Profile identifies 3 different skills: response, discrimination, and identification.
LittlEars[29]	0-35	The LittlEARS® Auditory Questionnaire [Coninx 2009]
Speech production		
MAIS [29]	0-36	Meaningful Auditory Integration Scale [Zimmerman-Phillips]
CSIM[30]	0-100%	Children's Speech Intelligibility Measure
BIT[30]	0-100%	Beginners' Intelligibility Test
GFTA-2[30]	Stnd for age	Goldman-Fristoe Test of Articulation - Second edition. Mean (SD):100 (15)
PCC[30]	0-100%	Percentage consonants correct
PVC[30]	0-100%	Percentage vowels correct
Arabic speech intelligibility test[31]	0-100%	Children's speech intelligibility test using pictures resulting in an overall speech intelligibility score (%)
Auditory performance		
Composite test[38]	4-8	Composite test composed of One-Word Picture Vocabulary Test, Peabody Picture Vocabulary Test, Test of Comprehension of Grammar for Children, language production elicited by fTCD paradigm and sentence repetition task

Stnd: standardized

speech production[31], while 3 other studies did not for speech perception.[1,2,27] In adults with prelingual SNHL, Kraaijenga et al. found no significant difference in speech perception between left and right implantees.[1] Budenz et al. showed that right ear implanted adults performed better on CNC words and phonemes, while the City University of New York tests for speech perception in quiet and noise did not differ significantly.[21] Similarly, Kamal et al. observed a significant difference favoring the right CI in one of the three tests used.[25] Finally, Sharpe observed a significant REA for hearing in noise test scores after standardizing the scores, yet not for the CVC word and phoneme scores.[28]

Table 4 | Study outcomes for subjects with prelingual onset of SNHL

Study (year)	**Test**	**Study population**	**Sample size**		**Score post implantation**		***P* value**
			L	**R**	***L***	**R**	
Speech production							
Flipsen (2008)[30]	CSIM (%)	Pre- and postlingual children	5	10	19.5 (9.2)	43.0 (21.1)	.0433*
	BIT (%)				49.8 (24.6)	76.5 (25.2)	NS
	Conversational speech(%)				72.8 (13.9)	88.8 (13.4)	NS
	GFTA-2[†]				47.2 (12.6)	73.0 (18.8)	.0278*
	GFTA-2[‡]				60.0 (15.9)	94.7 (8.8)	.0034*
	PCC (%)				66.7 (11.4)	80.3 (12.1)	NS
	PVC (%)				91.7 (3.9)	94.3 (5.9)	NS
Mohammed & Sarwat (2015)[31]	Arabic Speech Intelligibility test	25 prelingual children	?[§]	?[§]	29.6 (11.6)	59.5 (20.5)	<.001*
Speech perception							
Henkin (2008)[23¶]	AB monosyllabic word (%)	Prelingual children	41	30	49 (35-64)	62 (50-80)	.025*
	AB phonemes (%)				74 (66-84)	82 (73-92)	.026*
Kamal (2014)[24]	Monosyllabic identification (%)	Prelingual children	14	14	80.8 (14.7)	96.1 (4.8)	.03*
	Minimal pairs (%)				79 (13)	92.8 (8.1)	.049*
	WIPI (%)				64.4 (36)	79.9 (14.6)	.23
Surmelioglu (2014)[29]	LIP	Prelingual children	35	28	39.8 (3.3)	40.3 (2.4)	NS
	MAIS				36.9 (3.1)	37.2 (2.6)	NS
	LittlEARS				31.2 (4.1)	32.3 (3.8)	NS
Kraaijenga (2015)[25]	CVC phoneme (%)	Prelingual adults	31	26	NR	NR	.232
Grammatical comprehension and speech production							
Chilosi (2014)[38]	Composite score of multiple tests	Prelingual children	7	13	4.7 (0.9)	6.7 (1.5)	.046*[††] .06[‡‡]

Data presented in mean and standard deviation unless otherwise noted. †: related to age; ‡: related to implant experience; §: total sample n=24 left, n= 26 right; ¶: Mean and 25th and 75th percentiles; ††: uncorrected; ‡‡: corrected for age of implantation; CSIM: Children's Speech Intelligibility Measure; BIT: Beginners' Intelligibility Test; GFTA-2: Goldman-Fristoe Test of Articulation - Second edition; PCC: Percentage Consonants Correct; PVC: Percentage Vowels Correct; AB: Arthur Boothroyd WIPI: Word Intelligibility by Picture Identification; LIP: Listening Progress Profile; MAIS: Meaningful Auditory Integration Scale; CVC; consonant-vowel-consonant; L: left; R: right; NS: not significant; NR: not reported; * p-values <.05 were deemed statistically significant.

Table 5 | Study outcomes for subjects with postlingual onset of SNHL

Study (year)	**Test**	**Who**	**Sample size**		**Score post implantation**		***P* value**
			L	**R**	**L**	**R**	
Speech perception							
Morris (2006)[1]	HINT sentence (%)		38	63	80	70	.57
	CUNY quiet (%)				90	79	.82
	CUNY noise (%)				85	73	.80
	CNC word (%)				49	45	.60
	CNC phoneme (%)				66	57	.45
	HINT sentence (%)	Sub analysis right-handed patients	24	43	76	68	.79
	CUNY quiet (%)				87	76	.92
	CUNY noise (%)				78	69	.58
	CNC word (%)				45	43	.64
	CNC phoneme (%)				64	59	.60
Budenz (2011)[20†‡]	CUNY quiet (%)	Sub analysis age ≥ 70 years	22	38	77	90	.075
	CUNY noise (%)				62	77	.05
	CNC word (%)				45	57	.03*
	CNC phoneme (%)				45	57	.02*
Roberts (2012)[27§]	CNC (%)		56	57	53.7 (0.42)	54.3 (0.41)	.88
Kamal (2014)[24]	4 choice spondee (%)		20	20	78.8 (23)	91.7 (16.2)	.12
	High context sentence (%)				40.2 (37.1)	62.7 (34.6)	.12
	Monosyllabic identification (%)				27.5 (25.6)	48.7 (23)	.02*
Mosnier (2014)[18§]	Disyllabic words:		43	50			
	-SNR 0 dB (%)				12 (2.8)	25 4.7)	<.005*
	-SNR 5 dB (%)				23 (3.7)	34 (3.2)	<.05*
Kraaijenga (2015)[25]	CVC phoneme (%)		182	189	NR	NR	.867
Sharpe (2016)[28†]	HINT (%)		44	52	NR	NR	NS
	CVC phoneme (%)						NS
	CVC word (%)						NS
	HINT (%)	Sub analysis age > 59 years	32	29	75 (22)	84 (18)	.06
	HINT (stnd)* (%)				77 (21)	86 (21)	.04*
	CVC phoneme (%)				65 (21)	68 (18)	.25
	CVC words (%)				45 (22)	52 (19)	.10
	HINT (%)	Sub analysis age 18 – 52 years	12	23	80 (23)	77 (33)	.39
	HINT (stnd)*(%)				83 (24)	78 (37)	.33
	CVC phoneme (%)				72 (14)	61 (29)	.10
	CVC word (%)				52 (21)	52 (21)	.50
Speech production							
Mohammed & Sarwat (2015)[31¶]	Arabic Speech Intelligibility (%)	25 incl. adolescents	¶	¶	32.5 (12.8)	74.8 (16.1)	<.001*

Data presented as mean score with standard deviation unless otherwise noted. †: scores extracted from figures; ‡: standard error of mean (SEM) not accurately extractible; §: mean (SEM); ¶: total sample n=24 left, n= 26 right; L: left; R: right; NR: not reported; NS: not significant; HINT: Hearing in noise test; CUNY: City University of New York; CNC: consonant-nucleus-consonant; SNR: speech noise ratio; CVC; consonant-vowel-consonant; stnd: standardized; Four Choice Spondee test: closed-set; High Context Sentence test: closed-set with open end; * *p*-values <.05 were deemed statistically significant.

Handedness

Two studies performed a sub analysis on handedness. In concordance with their overall results, Morris et al. found no difference between left ear and right ear implantees in a subgroup of right-handed patients.[2] Henkin et al.,[24] who found a significant REA in the whole patient group, also performed a sub analysis on the right-handed patients and found that the significantly better performance of right-implanted children compared to left-implanted children was preserved in their right-handed patients (words: F(1,58)=9.24, *p*=.003; phonemes: F(1,58)=8.32, *p*=.005). In addition, they performed a multivariate analysis in all patients and found no effect of dominance (e.g. compatibility between dominant hand and side of CI: left-handed with left CI vs. right-handed with right CI) on speech perception performance (words, *p*=.84; phonemes, *p*=.65).[24]

DISCUSSION

Since the lateralization in the NH brain is already so complex and impressionable, this raises the question if, and how, the phenomenon "REA" in NH subjects can be translated to the situation of patients with SNHL and a CI. There is evidence that hearing loss affects the REA differently dependent on whether the onset of hearing loss was prelingually or postlingually. Early auditory deprivation in children has shown to cause an atypical organization of the auditory nervous system.[35,36] Through functional transcranial Doppler ultrasonography hemisphere lateralization in unilaterally implanted children with symmetrical SNHL (n=20) was studied.[37] Thirteen children had a right CI, of which the majority (77%) demonstrated left hemisphere dominance. Seven children had a left CI. Interestingly, 3 of the 4 left ear implanted children with age at implantation below 3 years, showed right hemisphere dominance for speech perception. The remaining child had an inconclusive result. In contrast, the two later left ear implanted children (> 8 years) developed ipsilateral left hemisphere dominance. The authors suggest that unilateral reafferentation of the left ear can induce reorganization of language functions in the right hemisphere when it takes place in a critical period early in life when the brain is (still) plastic.[37] Plasticity of the brain is maximal in the first 3.5 years of life.[35,36] Consequently, with a right ear implant or later implantation of the left ear, the established patterns of left hemisphere dominance are preserved. Similar results were seen in a study by Henkin et al., in which speech perception and speech processing patterns were compared between right ear and left ear implanted children. Although speech perception was equal between both groups, speech processing patterns assessed with low-resolution electromagnetic tomography were similar to NH subjects for the right ear implanted children (bilateral temporal lobe) whereas enhanced ipsilateral temporal lobe activation was seen in the left ear implanted children.[38] These results suggest that the left ear implanted children's brains adapted to unilateral auditory input in the left ear and consequently reafferentation took place to ensure sufficient input to the dominant left hemisphere.

Such altered patterns of input (increased ipsilateral and decreased contralateral processing of speech compared to NH subjects) have been demonstrated in adults with unilateral SNHL as well.[39,40] In these adults an increase in ipsilateral activation of the auditory cortex was seen on the dominant left side. In children with unilateral SNHL, worse verbal and non-verbal performance with right-sided, unilateral SNHL compared to left-sided, unilateral SNHL have been described[41,42], indicating that it is the right ear that adds the greatest contribution to speech perception.

In this systematic review we provide an overview of studies that investigated the influence of side of implantation on speech and language outcomes after unilateral cochlear implantation. Four out of six pediatric studies found a REA in one or more outcome measures. Five out of eight adult studies found a REA in one or more outcome measures. Overall, in both children and adults there is proof of a REA, although not indisputable because some studies do not see such a phenomenon and all studies are largely affected by confounding factors. One study found very large differences in speech production capabilities between left and right implantees.[31] Since this study was deemed to have a high risk of bias, these results are probably an overestimation. Another study, investigating prelingually deafened children, did not correct for possible confounders such as age at implantation.[29]

Two studies in this review analyzed the effect of handedness and found no difference in results compared to the results of the total group.[2,24] These findings are similar to the findings of Deguine et al. who retrospectively investigated the effect of dominance in 111 patients (children and adults).[22] Patients were dichotomized, based on CI implantation ipsilateral or contralateral to their dominant hand: left-handed + left ear implanted & right-handed + right ear implanted versus left-handed + right ear implanted & right-handed + left ear implanted. No differences in speech outcomes between groups were found. However, patients were not further sub divided into left-handed and right-handed patients and no adjustments were made for several potential confounders such as type of implant device, follow-up and age at implantation. Therefore this study was not included in this systematic review. To sum up results from these three studies, handedness does not seem to be an influential factor in the existence of the REA. This could be explained by the fact that left-handed patients predominantly have a left hemisphere dominance just as the majority of right-handed patients (70-80% versus 95-98%), therefore handedness did not greatly alter the effect of side of implantation.

As mentioned previously, the heterogeneity in the study populations is high, which is likely to have influenced the results. Furthermore, due to heterogeneity in outcome measures and a lack of reporting of measures of uncertainty, no pooled analysis could be performed. In addition, the used outcome measures may not be sufficiently specific to detect a REA. As described in the introduction, a REA is most evident in dichotic listening tests. These can however only be used in subjects who are able to receive auditory stimuli in both ears, which is evidently not possible for unilaterally implanted patients with symmetrical severe-to-profound SNHL. Consequently, various outcome measures in left-implanted and right-implanted patients were compared. Finally, due to the retrospective design of the majority of the studies it is not possible to correct for all the patient-related factors that may have influenced the observed outcome differences between patients with a left or right CI. A strength of this systematic review is the thorough systematic search of multiple databases with a broad search syntax and the extensive critical appraisal of the studies. Furthermore, we subdivided children and adults and incorporated the onset of acquisition of speech in the presentation and interpretation of the results.

CONCLUSION

This systematic review investigated the effect of side of implantation in subjects with symmetrical SNHL after receiving a CI. The results of this review, though the level of evidence of included studies was low, revealed evidence for a REA in prelingually deafened children as well as postlingually deafened adults. Moreover, none of the studies identified a left ear advantage. In view of these results, we suggest that right ear implantation may be beneficial over left ear implantation in case of symmetrical SNHL and in the absence of other prognostic factors. Furthermore, this will be the practical side for most (right-handed) patients.

CONFLICT OF INTEREST

The authors do not have any competing interests.

Key points

1. One hemisphere in the brain is of greater influence on several brain functions compared to the contralateral hemisphere. As such, a dominant left hemisphere is seen in 95-98% of right-handed and in 70-80% of left-handed normal hearing subjects for speech perception and speech production.
2. Although the auditory cortex receives auditory input from both ears, it is most strongly stimulated by the contralateral ear.
3. The combination of the assumptions described above results in a phenomenon called the right ear advantage, meaning that in the majority of normal hearing subjects the right ear is most important for the perception and production of speech.
4. The majority of studies in this systematic review found a right ear advantage in subjects with prelingual and postlingual sensorineural hearing loss (SNHL) after receiving a cochlear implant. No study found an advantage of a left-implanted cochlear implant over a right-implanted cochlear implant.
5. Given the results found in this systematic review, we cautiously advise implanting the CI in the right ear when other prognostic factors do not favor the left ear and SNHL is symmetrical.

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PART 2

Bilateral cochlear implantation

Chapter 4

Objective and subjective measures of simultaneous vs sequential bilateral cochlear implantation: A randomized clinical trial

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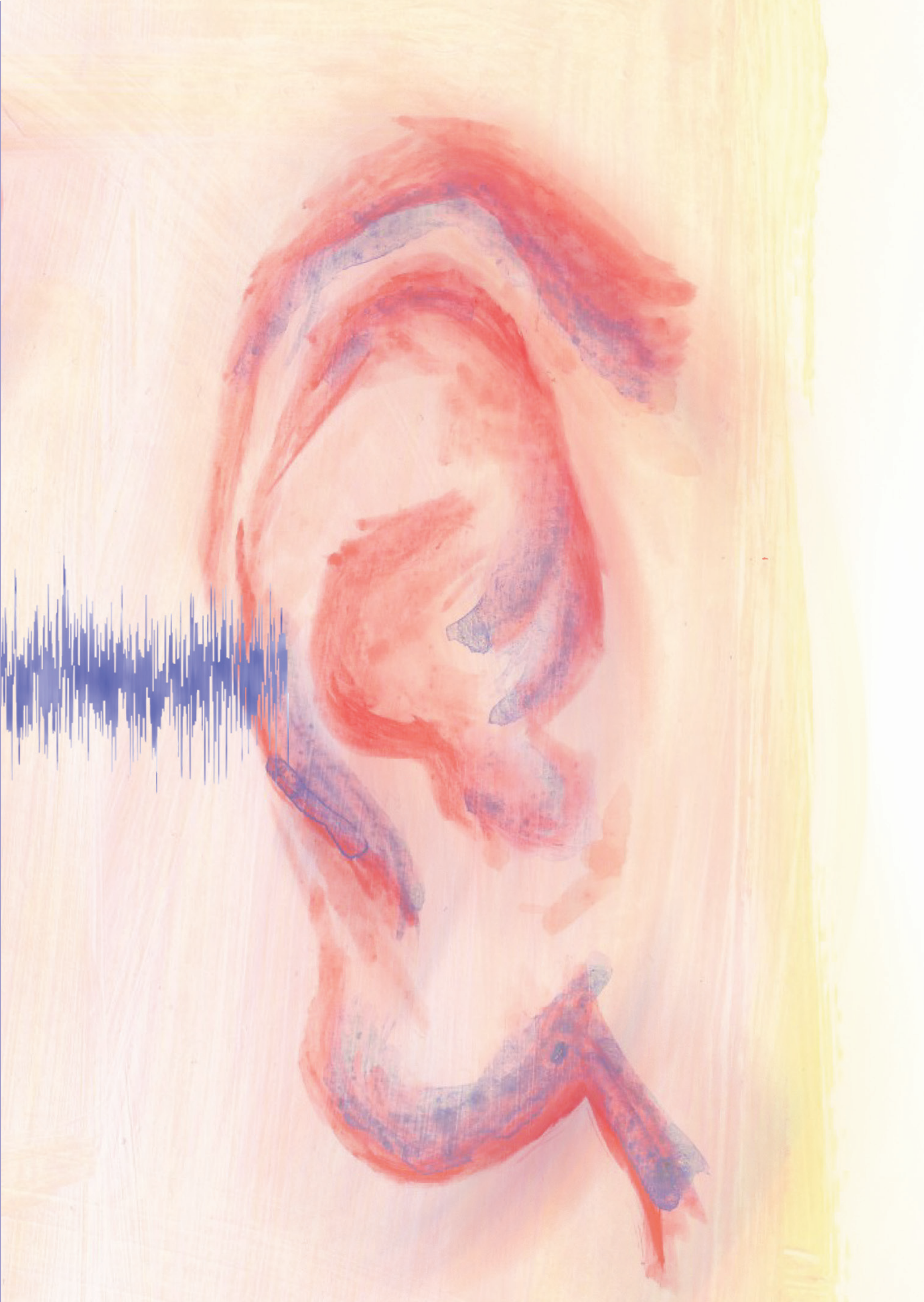

ABSTRACT

Importance: To date, no randomized clinical trial on the comparison between simultaneous and sequential bilateral cochlear implantation (BiCI) has been performed.

Objective: To investigate the hearing capabilities and the self-reported benefits after simultaneous BiCI compared with those after sequential BiCI.

Design, settings and participants: A multicenter randomized clinical trial was conducted between January 12, 2010, and September 2, 2012, at 5 tertiary referral centers among 40 participants eligible for BiCI. Main inclusion criteria were postlingual severe to profound hearing loss, age 18 to 70 years, and a maximum duration of 10 years without hearing aid use in both ears. Data analysis was conducted from May 24 to June 12, 2016.

Interventions: The simultaneous BiCI group received 2 cochlear implants during 1 surgical procedure. The sequential BiCI group received 2 cochlear implants with an interval of 2 years between implants.

Main outcomes and measures: First, the results 1 year after simultaneous BiCI were compared with the results 1 year after sequential BiCI. Second, the results of 3 years of follow-up for both groups were compared separately. The primary outcome measure was speech intelligibility in noise from straight ahead. Secondary outcome measures were speech intelligibility in noise from spatially separated sources, speech intelligibility in silence, localization capabilities, and self-reported benefits assessed with various hearing and quality of life questionnaires.

Results: Nineteen participants were randomized to simultaneous BiCI (11 women and 8 men; median age, 52 years [interquartile range, 36-63 years]), and another 19 participants were randomized to undergo sequential BiCI (8 women and 11 men; median age, 54 years [interquartile range, 43-64 years]). Three patients did not receive a second cochlear implant and were unavailable for follow-up. Comparable results were found 1 year after simultaneous or sequential BiCI for speech intelligibility in noise from straight ahead (difference, 0.9 dB [95% CI, −3.1 to 4.4 dB]) and all secondary outcome measures except for localization with a 30° angle between loudspeakers (difference, −10% [95% CI, −20.1% to 0.0%]). In the sequential BiCI group, all participants performed significantly better after BiCI on speech intelligibility in noise from spatially separated sources and on all localization tests, which was consistent with most of the participants' self-reported hearing capabilities. Speech intelligibility-in-noise results improved in the simultaneous BiCI group up to 3 years following BiCI.

Conclusion and relevance: This study shows comparable objective and subjective hearing results 1 year after simultaneous BiCI and sequential BiCI with an interval of 2 years between implants. It also shows a significant benefit of sequential BiCI over unilateral cochlear implantation. Until 3 years after simultaneous BiCI, speech intelligibility in noise significantly improved compared with previous years.

Key words

cochlear implantation; bilateral; sequential; simultaneous; bimodal; randomized controlled trial; evidence based medicine; speech perception; speech localization; quality of life; quality of hearing; hearing loss; deaf

INTRODUCTION

Various observational studies have shown that individuals who receive bilateral cochlear implants (CIs) are better able to localize sounds and perceive speech in noise than are patients who receive a unilateral implant.[1-4] These findings were recently confirmed in a randomized clinical trial (RCT) on the effectiveness of simultaneous bilateral cochlear implantation (simBiCI) compared with unilateral cochlear implantation (UCI), which showed that participants who receive bilateral CIs benefit in difficult listening situations when speech and noise are spatially separated and in various localization tests.[5] The results remained stable for at least 2 years of follow-up.[6]

Although the rate of deaf adults receiving bilateral CIs is increasing, the question remains whether simBiCI lead to better hearing results than sequential BiCI (seqBiCI). Systematic reviews suggest that simultaneous BiCI may result in better postoperative outcomes than sequential BiCI in children and that a prolonged interval between implants may have a negative effect or, at best, no effect on postoperative outcomes in children.[7,8] Comparative studies on simultaneous vs sequential BiCI in adults have not been conducted, to our knowledge. The best available evidence to date are the previously mentioned observational studies that show that both simultaneous and sequential BiCI result in better postoperative outcomes compared with a unilateral cochlear implant.[1-5] The outcomes of the studies are, however, difficult to compare since a great deal of heterogeneity exists between the studies regarding study design, sample size, follow-up duration, and outcome measures.

The primary aim of this study was to compare the results of simultaneous BiCI with sequential BiCI with a 2-year interval between implants in adults with severe to profound postlingual sensorineural hearing loss. The secondary aim was to evaluate the results of 3 consecutive years of follow-up for the sequential and the simultaneous BiCI groups separately.

METHODS

Ethical Considerations

The study was approved by the Human Ethics Committees of all participating centers (University Medical Center [UMC] Utrecht, Maastricht UMC, Radboud UMC, Leiden UMC, and UMC Groningen) (NL2466001808), was registered in the Dutch Trial Register (NTR1722), and conducted according to the Declaration of Helsinki.[9] Written informed consent was obtained from all participants.

Study Design

We conducted a multicenter RCT to compare the hearing results after simultaneous BiCI with the hearing results after sequential BiCI in adults with severe to profound bilateral postlingual sensorineural hearing loss. The full protocol is in Supplement 1. We reported data according to the CONSORT statement.[10]

Between January 12, 2010, and September 2, 2012, all participants eligible to participate in this study were discussed, and inclusion and exclusion criteria for each participant were verified.[5] The inclusion criteria were as follows: (1) age of 18 to 70 years; (2) postlingual onset of sensorineural hearing loss; (3) pure-tone average hearing loss of 70 dB or higher in each ear; (4) duration of severe to profound hearing loss of less than 20 years in each ear and a difference in duration of deafness between the 2 ears of 10 years or less; (5) ability to hear with or without hearing aid until 10 years or less; (6) marginal hearing aid benefit, defined as an aided phoneme score of 50% or less at a 65-dB sound pressure level; (7) Dutch as native language; (8) willingness and ability to participate in all scheduled procedures; (9) general health allowing general anesthesia for the duration of potential simultaneous BiCI; (10) Dutch health insurance coverage; and (11) agreement to be implanted with Advanced Bionics implants. The exclusion criteria were as follows: (1) previous cochlear implant; (2) abnormal cochlear anatomy; and (3) chronic ear infections. After providing informed consent, undergoing hearing evaluations, and providing self-reported questionnaires on hearing and quality of life (QoL), participants were randomly allocated to 1 of 2 treatment groups. Using a web-based randomization program, participants were randomized to either receive bilateral Cis simultaneously or sequentially with an interval of 2 years between implants. We used a block randomization per center strategy to obtain an equal distribution between the sequential and simultaneous BiCI groups in all centers.

Intervention

All participants were implanted with HiRes90K implants (Advanced Bionics) and used Harmony processors (Advanced Bionics) with high resolution or high resolution 120 processing strategies. Implantation and rehabilitation (≥6 weeks) were performed in the participants' own hospitals, and rehabilitation decisions were based on the surgeon's and audiologist's expertise.

Hearing Evaluation

Hearing tests were conducted using the AB-York Crescent of Sound.[5,11] All tests were performed with bilateral CIs, except for participants in the sequential BiCI group prior to receiving their second cochlear implant. For these participants, we defined the *participant's preferred situation* as the maximum score reached either with cochlear implant only or cochlear implant plus hearing aid. When comparing follow-up years, we compared the results after sequential BiCI with the participant's preferred situation.

Primary and Secondary Outcomes

The primary outcome was speech intelligibility in noise from straight ahead, measured with the Utrecht–Sentence Test with Adaptive Randomized Roving levels,[12] which resulted in a speech reception threshold in noise. A speech reception threshold in noise of 30 dB was considered relative silence and was used as a cutoff if participants scored 30 dB or higher on all speech-in-noise tests.

Speech intelligibility in noise from spatially separated sources (SISSS) was an objective secondary outcome. Sentences were presented from 60° to the left (–60° azimuth) or to the right (+60° azimuth) of the participant, and the noise was presented from the opposite side.[13] When sounds come from different directions, participants usually have a best performing situation and a worst performing situation. A participant's best performing situation was defined when speech was presented to the ear with the lowest signal to noise ratio (SNR) and noise to the ear with the highest SNR. In participants' worst performing situations, speech and noise originated from the opposite sides. In the sequential BiCI group, before the implantation of the second cochlear implant, the best performing situation was defined as the situation in which the sound was presented to the implanted ear and the noise to the nonimplanted ear. After BiCI, the ear with the lowest SNR was defined as the best performing cochlear implant's side. Another objective secondary outcome was maximum speech intelligibility in silence, measured with the Dutch consonant vowel consonant test at varying decibel sound pressure levels. A third objective secondary outcome was localization capabilities in a setup with horizontally placed loudspeakers in an arc around the participant. Numbers were shown on screens, representing the loudspeaker above them. Thirty phrases were presented randomly at 60-, 65-, or 70-dB sound pressure level from one of the loudspeakers. Participants were instructed to face the loudspeaker in front during the procedure. The results were the percentage of correct responses in the following 3 localization conditions: 15° angle azimuth between loudspeakers (–30°, –15°, 0°, 15°, and 30°); 30° angle azimuth between loudspeakers (–60°, –30°, 0°, 30°, and 60°); and 60° angle azimuth between loudspeakers (–60°, 0°, and 60°).

Subjective secondary outcomes were self-reported benefits assessed with different quality of hearing questionnaires. The first was the Speech, Spatial and Qualities Hearing Scale (SSQ), which consists of 3 domains: speech (SSQ1), spatial hearing (SSQ2), and quality of hearing (SSQ3).[14] The second was the Nijmegen Cochlear Implant Questionnaire (NCIQ), which assesses 6 subdomains of hearing,[15] and the third was the visual analog scale (VAS) on hearing.

The QoL questionnaires were the VAS on health, the Health Utilities Index 3 (HUI3),[16] the Dutch EuroQol 5-Dimension questionnaire (EQ-5D),[17,18] and the Time Trade-off (TTO), calculated as a percentage using the following equation: [(life expectancy − amount of years to give up for perfect hearing)/life expectancy] × 100.[19]

Sample Size Calculation

To detect a clinically relevant difference of 3 dB in SNR between groups on the Utrecht–Sentence Test with Adaptive Randomized Roving levels and a SD of 3 dB, an α level of .05, and a power of 80%, 14 participants per group were needed. To compensate for any loss to follow-up, 5 additional participants were included per group.

Statistical Analysis

Statistical analysis was conducted from May 24 to June 12, 2016. Before analysis, all data were double-checked by 2 independent individuals. Most of the data were not normally distributed. We thus calculated median values and interquartile ranges. We used the Mann-Whitney test to compare the 1-year results from the simultaneous BiCI group with the 3-year results from the sequential BiCI group (1 year after sequential BiCIs). All analyses were 2-tailed, and a $P < .05$ was considered statistically significant. We used the Wilcoxon signed rank test to compare the 3-year results with the 1-year and 2-year results for the simultaneous and sequential BiCI groups separately, and we used Bonferroni correction for multiple testing. Median difference data were reported, including a 95% CI derived from the Hodges-Lehmann estimate in SPSS, version 22 (SPSS Inc).

Missing Data

In case of loss to follow-up in either group, we performed a per protocol (PP) analysis and a last observation carried forward (LOCF) analysis in which missing data were replaced by the participant’s last results before dropout. This analysis meant that unilateral scores were used for the sequential BiCI results after 3 years of follow-up in participants unavailable for follow-up.

RESULTS

Participant Characteristics

A total of 19 participants were included in each group. Baseline characteristics are described in Table 1. Hearing aid use before implantation was imbalanced between groups (sequential BiCI group, 19 participants; simultaneous BiCI group, 15 participants). Linear regression analysis revealed no confounding role of hearing aid use ($t36 = 0.05$; $P = .96$).

Loss to Follow-up and Missing Data

After providing written informed consent, 1 participant in each group withdrew and was replaced by new participants. One of the participants who withdrew had received a diagnosis of Kahler disease, and 1 preferred to be implanted with another brand of cochlear implant. During the second and third year, 2 participants in the sequential BiCI group withdrew because of personal reasons. Another participant was excluded from the sequential BiCI group because of poor results with the first implant and low expectations after sequential BiCI owing to central deafness caused by rhesus antagonism (Figure 1).

At 1 year after implantation, the 15° localization results were missing for 1 participant in the simultaneous BiCI group. At 3 years after implantation, the TTO result was missing for 1 participant in the sequential BiCI group, and the VAS on health and hearing was missing for another participant in the sequential BiCI group. A cutoff of 30 dB was used for the speech reception threshold for 1 participant in each group.

Simultaneous vs Sequential BiCI

Objective Results

As shown in the PP data in Table 2 and Figure 2, no significant differences were seen between the 1-year results in the simultaneous BiCI group and the 3-year results in the sequential BiCI group for all objective outcomes except for the 30° localization task. In the PP and LOCF analyses, the participants in the simultaneous BiCI group performed significantly better than those in the sequential BiCI group (PP: difference, –10% [95% CI, –20.1% to 0%]; LOCF: difference, –13.3% [95% CI, –23.3% to –3.3%]).

Subjective Results

As shown in the PP data in Table 2, Figure 3 and Figure 4 no significant differences were seen in the PP and the LOCF analyses on all subjective results between both groups. The score for the simultaneous BiCI group, although higher on all questionnaires except for 2 subdomains of the NCIQ, were not significantly different from the sequential group scores.

Sequential BiCI: Comparing Follow-up Years

Objective Results

As shown in Figure 2, participants in the sequential BiCI group performed better 1 year after receiving their second cochlear implant compared with previous years. A significant benefit was seen on the SISSS in the worst performing situation (difference between year 1 and year 3, –6.8 dB [97.5% CI, –10.5 to –3.4 dB]; difference between year 2 and year 3, –7.3 dB [97.5% CI, –13.7 to –1.1 dB]), as well as in the best performing situation (difference between year 1

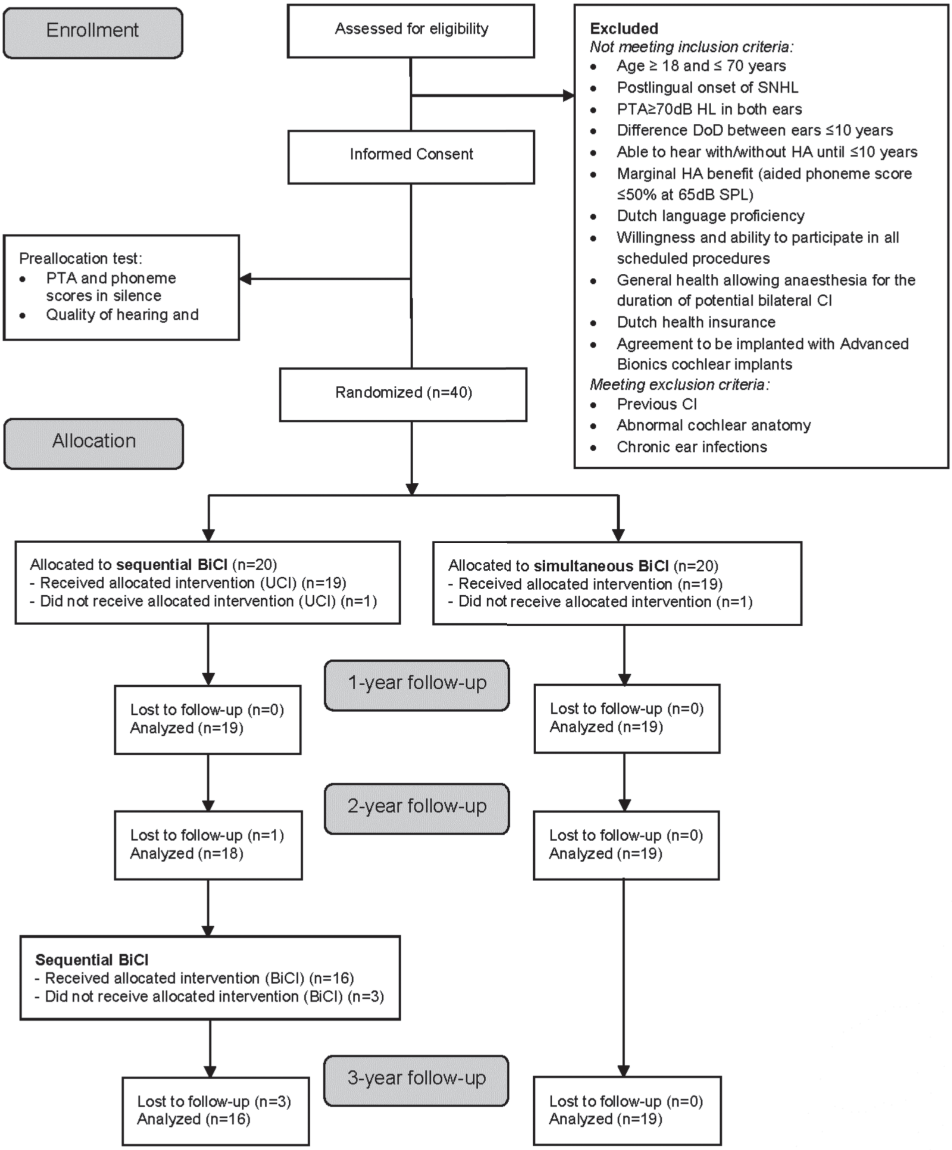

Figure 1 | Flowchart of enrollment

Table 1 | Baseline characteristics

	Sequential BiCI	**Simultaneous BiCI**
Male:Female	11:08	08:11
Age at inclusion (yrs)	54 [43-64]	52 [36-63]
Duration of severe HL AD (yrs)	17 [9-33]	16 [11-25]
Duration of severe HL AS (yrs)	18 [9-35]	16 [11-25]
First CI: Right:left	6:13	17:2
PTA AD (dB)	106 [94-111]	106 [89-119]
500Hz	90 [75-95]	95 [75-105]
1000Hz	95 [90-110]	100 [85-115]
2000Hz	100 [95-115]	110 [90-130]
4000Hz	120 [110-130]	115 [95-130]
PTA AS (dB)	108 [93-114]	108 89-120]
500Hz	90 [80-95]	90 [80-100]
1000Hz	100 [85-110]	100 [90-115]
2000Hz	110 [100-115]	115 [90-130]
4000Hz	115 [105-130]	120 [90-130]
Max. phoneme score with hearing aids (%)	44 [29-56]	48 [24-63]
Hearing aid use before CI yes: no	19:0	15:4
HA use year 1	12:7	N.A.
HA use year 2	13:5 (1 LTFU)	N.A.
Treatment Hospital		
Utrecht	11	8
Maastricht	4	5
Nijmegen	2	3
Leiden	1	2
Groningen	1	1
Cause of deafness		
Hereditary	7	9
Unknown and progressive	9	6
Sudden Deafness	0	2
Head trauma	0	1
Meningitis	2	0
Rhesus Antagonism	1	0
Sound exposure	0	1

Table 2 | Comparison between simultaneous BiCI and sequential BiCI for all outcome measures – per protocol and last observation carried forward analyses[a]

	BiCI, Median (IQR)		Difference (95% CI)	
	Sequential	**Simultaneous**	**PP**	**LOCF**
Objective tests for hearing, dB				
Speech intelligibility in noise from straight ahead	8.0 (5.5 – 12.7)	7.5 (3.8 – 12.2)	0.9 (-3.1 – 4.4)	0.9 (-2.8 – 4.4)
SISSS				
-Best performing situation	2.7 (0.1 – 7.8)	5.0 (-1.3 – 8.8)	-0.3 (-5.0 – 4.1)	-0.3 (-4.7 – 4.1)
-Worst performing situation	7.3 (4.8 – 12.1)	5.3 (0.3 – 13.1)	1.9 (-4.4 – 6.6)	2.5 (-3.1 – 6.6)
Localization, %				
-15°	51.7 (36.7 – 63.3)	53.3 (46.7 – 67.5)	-3.3 (-16.7 – 6.7)	-10.0 (-20.0 – 3.3)
-30°	60.0 (53.3 – 72.5)	76.7 (60.0 – 83.3)	-10.0 (-20.1 – 0.0)	-13.3 (-23.3 - -3.3)[b]
-60°	91.7 (76.7 – 99.2)	96.7 (86.7 – 100.0)	-3.3 (-13.3 – 0.0)	-6.7 (-13.3 – 0.0)
Maximum CVC phoneme score, %	90.0 (83.5 – 94.0)	88.0 (80.0 – 95.0)	1.5 (-4.0 – 8.0)	2.0 (-4.0 – 7.0)
Subjective hearing				
SSQ				
-Speech	43.7 (34.5 – 60.1)	59.4 (35.3 – 65.7)	-8.2 (-22.7 – 3.6)	-8.2 (-22.7 – 3.6)
-Spatial	51.8 (37.4 – 70.5)	59.2 (43.3 – 72.4)	-4.6 (-17.2 – 8.5)	-5.2 (-17.9 – 7.6)
-Quality	60.8 (50.5 – 67.8)	62.4 (58.2 – 80.0)	-7.1 (-17.6 – 4.6)	-6.3 (-17.6 – 4.6)
NCIQ				
Basic sound perception	86.3 (76.3 – 97.5)	92.5 (72.5 – 95.0)	-2.5 (-10.0 – 5.0)	-2.5 (-10.0 – 5.0)
Advanced sound perception	55.0 (40.0 – 77.5)	60.0 (45.0 – 85.0)	-2.5 (-20.0 – 10.0)	0.0 (-17.1 – 15.0)
Speech production	86.3 (76.3 – 97.5)	92.5 (80.0 – 95.0)	-2.5 (-10.0 – 5.0)	-2.5 (-12.5 – 2.5)
Self esteem	70.0 (55.6 – 82.5)	75.0 (65.0 – 80.6)	-5.0 (-16.1 – 3.9)	-5.0 (-15.0 – 4.4)
Activity limitations	76.3 (60.0 – 89.4)	75.0 (71.9 – 83.3)	0.0 (-13.9 – 10.0)	0.0 (-10.0 – 11.5)
Social interactions	66.9 (50.6 – 78.8)	63.9 (61.1 – 77.8)	-2.8 (-13.9 – 7.8)	-2.8 (-11.4 – 7.5)
VAS hearing	74.5 (61.3 – 80.0)	80.0 (70.0 – 85.0)	-5.0 (-10.0 – 4.0)	-5.0 (-10.0 – 3.0)
Subjective health				
VAS health	80.0 (71.0 – 90.0)	80.0 (65.0 – 90.0)	0.0 (-9.0 – 10.0)	0.0 (-6.0 – 10.0)
HUI3	0.78 (0.54 – 0.82)	0.78 (0.61 – 0.85)	-.024 (-.084 – .048)	0.0 (-.072 – .154)
EQ5D questionnaire				
Utility score	1.0 (0.8 – 1.0)	1.0 (0.8 – 1.0)	.00 (-.04 – .00)	0.0 (0.0 – 0.0)
Thermometer	80.0 (71.3 – 90.0)	75.0 (70.0 – 95.0)	1.0 (-5.0 – 10.0)	3.0 (-5.0 – 10.0)
Time trade off	100 (88.8 – 100)	100 (100 – 100)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)

BiCIs, bilateral cochlear implants; CVC, consonant vowel consonant; EQ-5D, Dutch EuroQol 5-Dimension; HUI3, Health Utilities Index 3; IQR, interquartile range; LOCF, last observation carried forward analysis; NCIQ, Nijmegen Cochlear Implant Questionnaire; PP, per protocol analysis; SISSS, Speech intelligibility-in-noise from spatially separated sources; SSQ, Speech, Spatial and Qualities Hearing Scale; VAS, visual analog scale. a Legend data contain 1-y results of the simultaneous BiCI group vs 3-y results of the sequential BiCI group. b P < .05.

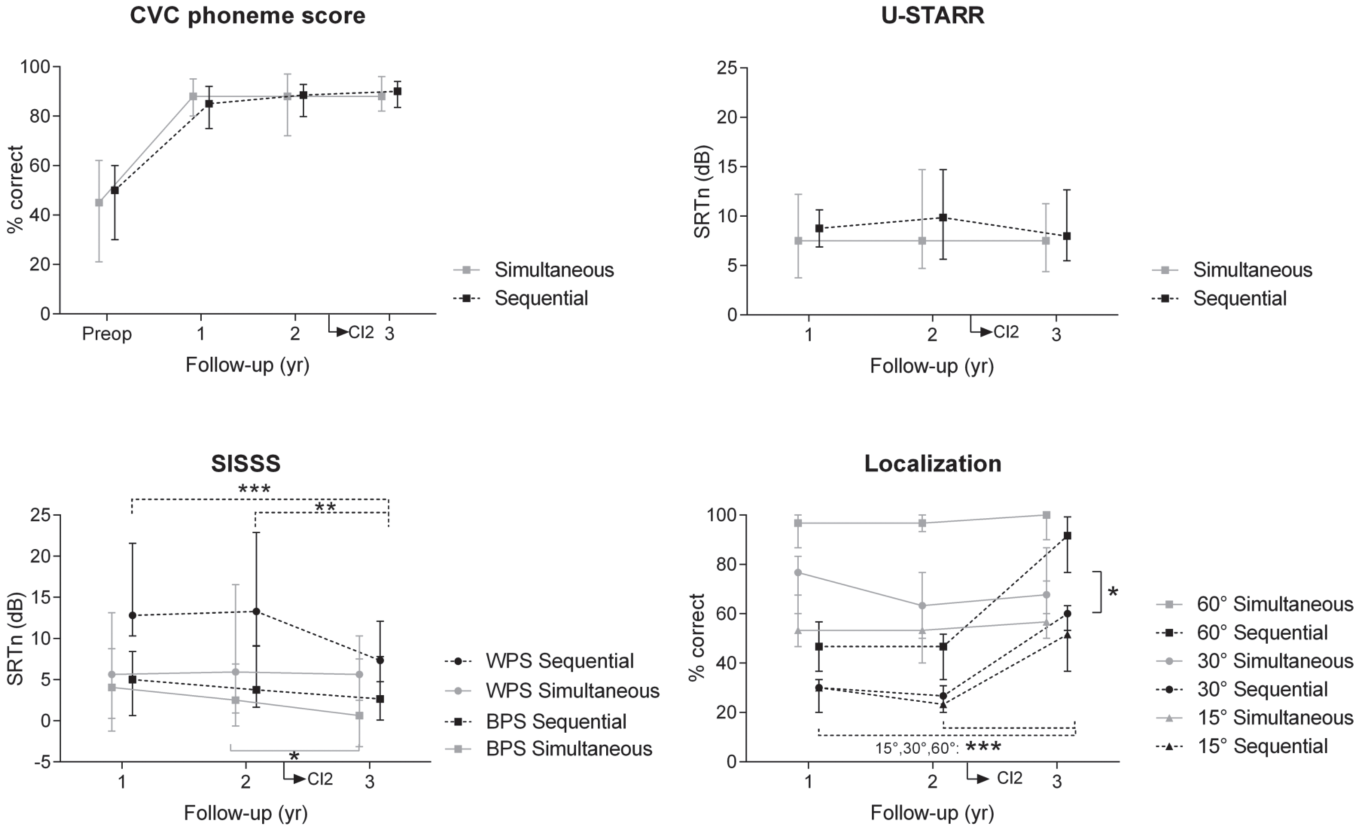

Figure 2. Development over time of objective outcomes for simultaneous and sequential bilateral cochlear implants

Scores of the per protocol data are presented in median values with an error bar representing the interquartile range. U-STARR: Speech intelligibility-in-noise test from straight ahead using the Utrecht - Sentence Test with Adaptive Randomized Roving levels; SISSS: Speech intelligibility-in-noise from spatially separated sources; WPS: worst performing situation; BPS: best performing situation; CVC: consonant vowel consonant (phoneme score); yr: year; CI: cochlear implant; preop: preoperative; The asterisks represent significant difference: *: p<.05, **: p<.01, ***: p<.001. Statistical analyses were performed between the 1 or 2-year data and the 3-year data, applying a Bonferroni correction. 30° localization capabilities did not significantly decrease during follow-up for the simultaneous BiCI group.

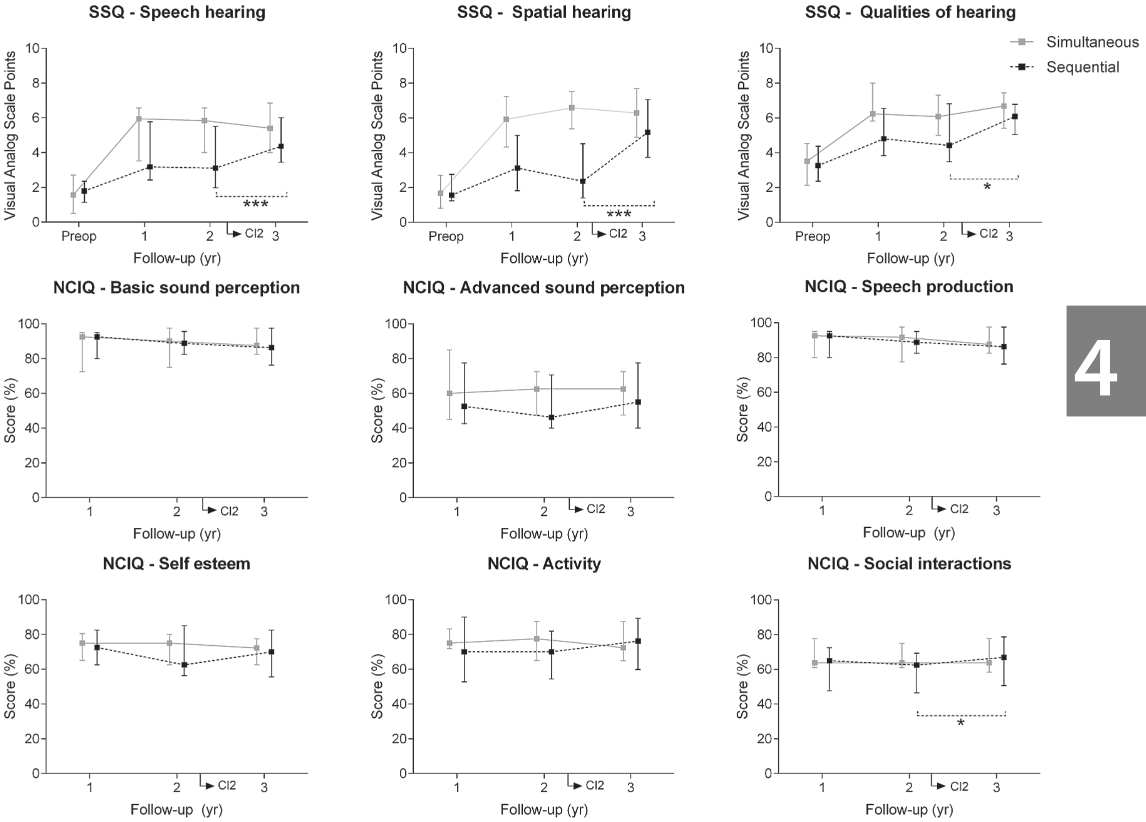

Figure 3 | Development over time of subjective outcomes for simultaneous and sequential BiCI

Scores of the per protocol data are presented in median values with an error bar representing the interquartile range. SSQ: Speech, Spatial and Qualities Hearing Scale; NCIQ: Nijmegen Cochlear Implant Questionnaire; yr: year; CI: cochlear implant; preop: preoperative; The asterisks represent significant difference: *: p<.05, **: p<.01, ***: p<.001. Statistical analyses were performed between 1-year, 2-year and 3-year data, applying a Bonferroni correction.

and year 3, –2.6 dB [95% CI, –4.7 to –0.2 dB]), which lost its significance after correction for multiple testing (–2.6 dB [97.5% CI, –5.2 to 0.3 dB]). In addition, participants in the sequential BiCI group performed better on all localization tests compared with the previous years (15° configuration: difference between year 1 and year 3, 23.3% [97.5% CI, 6.7%-36.7%]; difference between year 2 and year 3, 26.7% [97.5% CI, 13.3%-40.0%]; 30° configuration: difference between year 1 and year 3, 33.3% [97.5% CI, 21.7%-43.3%]; difference between year 2 and year 3, 35.8% [97.5% CI, 25.0%-46.7%]; 60° configuration: difference between year 1 and year3, 43.3% [97.5% CI, 28.3%-50.0%]; difference between year 2 and year 3, 43.3% [97.5% CI, 31.7%-53.2%]). No differences were seen for speech in noise from straight ahead and speech in silence.

Subjective Results

As shown in Figure 3, participants in the sequential BiCI group scored significantly better on the SSQ after receiving their second cochlear implant compared with previous years (difference on speech subscale between year 1 and year 3, 0.84 [97.5% CI, 0.12-1.48]; difference between year 2 and year 3, 0.64 [97.5% CI, 0.27-2.06]; difference on spatial subscale between year 1 and year 3, 2.01 [97.5% CI, 0.68-3.53]; difference between year 2 and year 3, 2.41 [97.5% CI, 1.45-3.97]; difference on quality subscale between year 1 and year 3, 1.09 [97.5% CI, 0.37-1.73]; difference between year 2 and year 3, 1.10 [97.5% CI, 0.05-1.85]).

On the NCIQ, participants scored significantly higher in year 3 on the social interactions subdomain compared with year 1 (difference, 5.5 [97.5% CI, 0.0-13.2]; P = .02). The difference between year 2 and year 3 (5.6 [95% CI, 0.3-11.7]) was not significant after correction for multiple testing. For the activity limitations subdomain, the differences between year 1 and year 3 (6.3 [95% CI, 1.5-12.5]) and year 2 and year 3 (7.2 [95% CI, 0.0-13.8]) were also not significant after correction for multiple testing.

As shown in Figure 4, no significant differences were seen on the results of the QoL questionnaires in the sequential BiCI group. Results of original data and LOCF data did not differ.

Simultaneous BiCI: Comparing Follow-up Years

When we compared the 3-year follow-up data with the 1-year and 2-year data for the participants in the simultaneous BiCI group, a significant improvement of –2.50 dB (97.5% CI, –4.85 to –0.01 dB) was seen for the best performing situation on the SISSS between year 1 and year 3. After correcting for multiple testing, we found that a 6.7% increase (97.5% CI, –0.01 to 15.0) in performance on the 15° localization task between year 2 and year 3 was not significant. No differences were observed for any of the other objective and subjective outcomes (Figures 2, 3 and 4).[5,6]

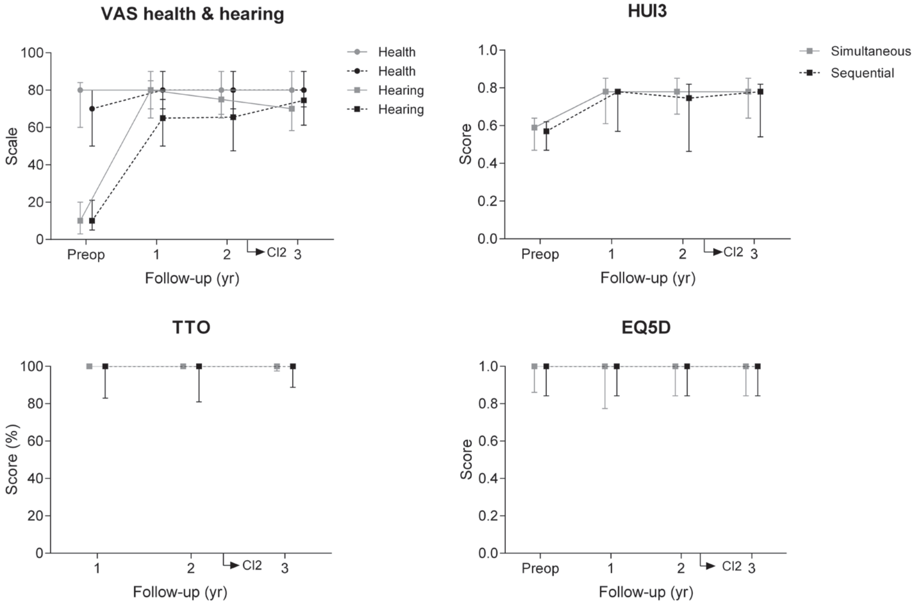

Figure 4 | Development over time of subjective outcomes on health for simultaneous and sequential BiCI

Scores of the per protocol data are presented in median values with an error bar representing the interquartile range. VAS: Visual Analogue Scale; HUI3: Health Utilities Index 3; EQ5D: Dutch EuroQol-5D; TTO: Time trade off; yr: year; CI: cochlear implant; preop: preoperative; The asterisks represent significant difference: *: p<.05, **: p<.01, ***: p<.001. Statistical analyses were performed between 1-year, 2-year and 3-year data, applying a Bonferroni correction.

DISCUSSION

In this study, we present the results of the first RCT, to our knowledge, comparing simultaneous and sequential BiCI in postlingually deafened adults. In addition, we present the 3-year follow-up results for both study groups separately.

First, the simultaneous BiCI group and the sequential BiCI group performed equally 1 year after BiCI on all objective and subjective hearing tests, except for the 30° localization task. The sequential BiCI group did not need a longer follow-up to reach the same level of speech perception as the simultaneous BiCI group. So far, studies have solely examined the benefit of BiCI versus UCI, but a comparison between sequential and simultaneous BiCI has not yet been attempted.[1,2,4] Because it requires auditory stimulation during early ages to achieve effective central auditory development, a critical period exists for pediatric cochlear implantation. Given this critical period, simultaneous BiCI has advantages over sequential

BiCI in children.[20] Simultaneous BiCI guarantees the implantation of the better ear and the earlier implantation of the second ear, which may facilitate the development of binaural hearing. In postlingually deafened adults, the auditory system is fully developed, which may explain the similar results between our 2 study groups.

Second, we found that the participants in the sequential BiCI group benefit from BiCI in the same listening situations as do the participants in the simultaneous BiCI group: difficult listening situations with speech and noise from spatially separated sources in participants' worst performing situation and on several localization tasks. These findings were confirmed by improved scores on questionnaires concerning perception of speech, spatial hearing, and quality of hearing (SSQ) and the social interaction subdomain on the NCIQ.

Two study participants dropped out of the sequential BiCI group for personal reasons. Both participants were satisfied with the results that they obtained with their first cochlear implant, which is in accordance with the significant improvement in QoL found in this study 1 year after a unilateral cochlear implant. However, sequential BiCI could further improve these participants' spatial hearing capabilities (hearing in noise from spatially separated sources and localization), as shown in this study.

Five earlier studies[21-25] investigated sequential BiCI compared with UCI. Two studies[21,25] compared bilateral results with unilateral results after sequential BiCI by deactivating 1 cochlear implant. This situation, however, is not representative for a unilateral cochlear implant because the patients are used to hearing with 2 cochlear implants and because cochlear implantation causes an insertion trauma that might have a negative effect on residual hearing. Ramsden et al[22] compared unilateral results prior to sequential BiCI with the results after sequential BiCI and found significantly improved scores after sequential BiCI. Improved hearing in quiet and noisy settings 3 months after sequential BiCI was also seen in a study by Zeitler et al.[24] In accordance with our results, Summerfield et al[23] reported subjective benefits of BiCI on the SSQ1, SSQ2, and SSQ3 but not on QoL questionnaires in a group of seqBiCI participants.

Finally, we saw an increase in speech-intelligibility-in-noise abilities in our simultaneous BiCI group 3 years after implantation. In a study by Eapen et al[26] with 9 individuals who received bilateral Cis simultaneously and fixed SNRs, hearing-in-noise results improved in the 4 years following implantation. Our simultaneous BiCI group exhibited an improvement in the SISSS results in the best performing situation (difference, –2.50 dB [95% CI, –4.69 to –0.32 dB]). This improvement may result from binaural integration, as measured through one of the binaural hearing effects: the squelch effect.[13]

Strengths and limitations

To our knowledge, this is the first RCT examining the effect of simultaneous vs sequential BiCI on various hearing outcomes. The use of this design minimized allocation bias. In addition, the study population was homogenous; for example, onset of hearing loss was not allowed to differ more than 10 years between ears. A longer interval between ears might have caused an unfavorable result in the sequential BiCI group owing to sound deprivation of the longer-deprived ear.[27] Three participants were unavailable for follow-up in the sequential BiCI group. We performed both a PP analysis and an LOCF analysis and found that this loss had no influence on the results. Owing to the multicenter nature of this study, implantation procedures may vary between centers. In addition, the sample size calculation incorporated loss to follow-up; therefore, the study had sufficient power to detect a difference on the primary outcome measure. However, the sample size might have been too small for secondary outcomes such as QoL questionnaires because smaller subjective changes were expected between the 2 groups. In addition, these questionnaires were unable to detect changes in QoL after cochlear implantation because they do not incorporate a specific hearing element. On 2 of these questionnaires (Time Trade-off, EuroQol 5-Dimension), ceiling effects were noted that hindered differentiation between study groups. Finally, this study focused solely on subjective and objective speech perception outcomes and did not incorporate other factors that affect the choice for simultaneous vs sequential BiCI, such as cost utility and surgical complications (such as bilateral areflexia).[28] We plan to study the differences between the first and second ear implanted in the sequential BiCI group and to investigate whether these participants demonstrate a clinically relevant binaural squelch effect.

CONCLUSION

In this RCT, we compared the objective and subjective results following simultaneous BiCI and sequential BiCI in adults with severe-to-profound hearing loss. This study demonstrates that individuals who receive bilateral CIs sequentially derive the same benefit as those who receive bilateral CIs simultaneously on speech perception 1 year after receiving their second cochlear implant. Participants who underwent sequential BiCI had significant improvements in spatial speech-in-noise and localization abilities compared with their unilateral situation before receiving a second cochlear implant. These findings were consistent with the participants' self-reported hearing capabilities. Three years after simultaneous BiCI, the spatial speech-in-noise abilities of the participants increased for the best performing situation. All other objective and self-reported hearing capabilities remained stable. These findings suggest that simultaneous BiCI offers long-term stable results in adults with severe-to-profound bilateral sensorineural hearing loss.

Conflict of interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Free reported receiving nonrestricted grants from Advanced Bionics and being sponsored by a neurotological stipendium from the Heinsius Houbolt Foundation. Dr Frijns reported receiving nonrestricted grants from Advanced Bionics and MedEl. Dr Mylanus reported receiving nonrestricted grants from MedEl, Cochlear, and Advanced Bionics. Dr Grolman reported receiving nonrestricted grants from Advanced Bionics, MedEl, Oticon, and Cochlear. No other disclosures were reported.

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KEY POINTS

Question Is there a difference between the hearing results after receiving simultaneous bilateral cochlear implants and the hearing results after receiving sequential bilateral cochlear implants with a 2-year interval between implants?
Findings In this randomized controlled trial including 38 participants, no differences were found on all objective and subjective outcome measures on hearing and quality of life. One year after receiving a second cochlear implant, significant improvements were seen on objective hearing in noise and localization results as well as subjective hearing results in the group that received sequential bilateral cochlear implants.
Meaning Patients who received sequential bilateral cochlear implants with a 2-year interval between implants derive the same benefit of a second cochlear implant as patients who received simultaneous cochlear implants.

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Chapter 5

Development of a Squelch Effect in Adult Patients After Simultaneous Bilateral Cochlear Implantation

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ABSTRACT

Objectives: To investigate whether a squelch effect occurs in the first 3 years following simultaneous bilateral cochlear implantation and to investigate whether this effect increases during follow-up.
Study design: Prospective study as part of a multicenter randomized controlled trial that compares simultaneous bilateral cochlear implantation to sequential bilateral and unilateral cochlear implantation.
Setting: Tertiary referral center.
Patients: Nineteen postlingually deafened adults.
Intervention: Simultaneous bilateral cochlear implantation.
Main outcome measure: The squelch effect, measured yearly with a speech-intelligibility-in-noise test with spatially separated sources. Bilateral results were compared to unilateral results in which the cochlear implant at the noise side was turned off. The squelch effect was investigated for the patients' best performing ear and for the left and right ears separately.
Results: In 13 individual patients, a squelch effect was present after 1 year. This number increased during follow-up years. On group level, a squelch effect was present in patients' best performing ear after 2 and 3 years (1.9 dB). A squelch effect was present in both ears after 3 years (AS: 1.7 dB, AD: 1.3 dB).
Conclusions: Patients who underwent simultaneous bilateral cochlear implantation developed a measurable benefit from the squelch effect after two years in their best performing ear and after three years in both ears. These observations suggest that the brain learns to use interaural differences to segregate sound from noise after simultaneous bilateral cochlear implantation. The squelch effect increased over time which suggests a growth in cortical integration and differentiation of inputs from bilateral CIs due to brain plasticity.
Trial Registration: Dutch Trial Register NTR1722

Key Words: Bilateral cochlear implantation, binaural hearing, cochlear implantation, cochlear implants, deafness, hearing loss, brain plasticity, signal-to-noise ratio, spatial hearing, speech in noise, squelch effect.

Level of evidence: 1b

INTRODUCTION

Cochlear implantation has become a widely accepted treatment for patients with severe to profound hearing loss who obtain limited benefit from conventional hearing aids (HAs). Although many patients with a single cochlear implant (CI) achieve relatively high levels of speech perception in silence, even the most successful implantees have difficulties with speech perception in noise. These difficulties may be overcome in bilaterally implanted patients by enabling binaural hearing due to sound input in both ears.[1–4]

Hearing with two ears, binaural hearing, is based on three principles: 1) the head shadow effect occurs in spatially separated speech and competing noise. The presence of the head results in differentiated signal-to-noise ratios (SNRs) between both ears due to differential filtering of sounds (high versus low frequency). With two functional ears a subject is able to attend to the ear with the most favorable SNR. 2) The binaural summation effect occurs when speech and noise originate from the same location. Binaural summation is the ability of the auditory system to combine input from both ears and to derive benefit from this combined information centrally. Binaural summation leads to increased perceived loudness of sounds. 3) The squelch effect occurs in spatially separated speech and competing noise situations. Squelch is the ability of the auditory system to combine the information from both ears centrally and segregate the speech from the noise by the differences in sound between both ears. Specifically, the brain is able to suppress the noise by utilizing this noise information derived from the ear with the poorer SNR. Through this segregation, a subject's speech perception in noise is improved.[5]

In the literature there is evidence suggesting that when listening with both ears, normal hearing listeners are able to perceive a 3-5 dB binaural squelch.[6–8] In normal and impaired hearing there are several psychophysical phenomena related to the squelch effect, which are the binaural masking level difference[9], comodulation masking release[10], in the order of 1.3 dB for speech, and spatial release from masking[11], in the order of 5.1dB for the best-aided bilateral condition. The terms refer to various implementations of test paradigms in which the perception of a tone or speech in one ear, presented in an interfering sound, is improved by presenting the interfering sound also to the other ear. The improvement is due to central auditory processing mechanisms, working on top of the other effects, summation and head shadow, known for improving binaural perception.

Binaural hearing is superior to monaural hearing in normal hearing listeners and bilateral HA users, which resulted in bilateral HA fitting as standard care two decades ago.[1,12,13] For bimodal CI users (e.g. combination of a CI and HA) the additional benefit of a HA is limited in patients with little to no residual hearing.[14–16] In a study with 35 bimodal patients with a consonant noun consonant HA score of 12.4 dB (13.9) no squelch effect was observed (-0.7 dB) in the CI ear.[11] Since speech perception is limited through the HA-ear, there is poor auditory information input to the brain from this ear, hampering a squelch effect in bimodal patients.

The squelch effect has also been investigated in bilateral CI users.[5,17–26] Most studies were retrospective cohort studies or cross-sectional studies with small sample sizes and study populations comprising a combination of simultaneously and sequentially implanted patients. Most of these studies demonstrated benefits of the head shadow and binaural summation effects, but limited evidence for the squelch effect. Two studies reported a lack of squelch effect after a follow-up period of six months.[21,26] In another study, a squelch effect was seen in 3 out of 10 simultaneously implanted patients after 1 year of follow-up.[17] Another study found a squelch effect after at least one month following sequential implantation in the left ear in a group of sequentially implanted patients, but not in the right ear.[22] Six months after implantation, a squelch effect was objectified in 50% of 34 simultaneously implanted patients.[24] In a study with 25 simultaneously and 1 sequential bilaterally implanted patients using fixed SNRs, a significant squelch effect was observed in the whole group after 1-year follow-up, which was not yet present after 6 months.[27] In a longitudinal study of nine simultaneously bilaterally implanted patients, an increase in the squelch effect was seen over a 4-year period.[28]

In literature generally two test set-ups are used: 1) a set-up with speech from straight ahead (0^o azimuth) and noise from the side ($+90^o$ azimuth and -90^o azimuth) and 2) a set-up with speech from one side (45 or 60^o azimuth) and noise from the other side (-45^o or -60 azimuth).[21,26] The second set-up is less sensitive to estimate the head shadow effect but more sensitive to detect the binaural squelch effect.[2] The squelch effect can be expressed in two ways. First, if measured at a fixed SNR of 10dB, the squelch effect is expressed as an increase in percentage correct scores at 10dB SNR. Second, it can be expressed as the gain in the speech reception threshold in noise (SRTn), which is the SNR at which patients score 50% of sentences correctly.[22]

In our prospective study, we investigated the presence of the squelch effect in 19 simultaneously bilaterally implanted CI users after a follow-up of 3 years. The aim of this study is twofold: to evaluate if there is an apparent squelch effect in simultaneously bilaterally implanted patients and to evaluate if there is an increase in the squelch effect due to what we would normally call cochlear implant users' learning curve but is in fact central adaptation due to brain plasticity.[29]

MATERIAL AND METHODS

Study design and participants

The current study was embedded in a multicenter randomized controlled trial (RCT) comparing simultaneous bilateral and sequential bilateral and unilateral cochlear implantation in adults with severe bilateral postlingual sensorineural hearing loss.[4] The University Medical Center (UMC) Utrecht designed and coordinated this RCT. Inclusion and treatment of patients was done in collaboration with Maastricht UMC, Radboud UMC, Leiden UMC and UMC Groningen.

Thirty-eight patients were randomized to either 1) sequential bilateral cochlear implantation or 2) simultaneous bilateral cochlear implantation. All patients were implanted with Advanced Bionics HiRes90K® CIs and used Harmony speech processors. For more detailed information concerning the study protocol of this RCT we refer to the previous article of our study group.[4] In the current study, we evaluated the squelch effect in the 19 simultaneously bilaterally implanted patients during 3 years of follow-up. Data were reported according to the CONSORT statement. The study was approved by the Human Medical Ethics Committees of all participating centers (NL2466001808), registered in the Dutch Trial Register (NTR1722) and conducted according to the principles expressed in the Declaration of Helsinki.

Test set-up

The speech intelligibility-in-noise with spatially separated sources (SISSS) test was conducted using the AB-York crescent of sound test set-up, which included the Utrecht-Sentence Test with Adaptive Randomized Roving levels (U-STARR).[30]

Sentences were presented from 60° azimuth to the left and speech-shaped noise from 60 degrees azimuth to the right of the subject (S-60 N+60) or reversed (S+60 N-60) (see Figure 1). We chose this set-up since this is the most realistic representation of the everyday listening situations in noise in which a subject will turn their head with their best ear towards the signal and their worst ear towards the noise. In addition, this set-up is more sensitive to detect a squelch effect. A sentence was scored as correct when a subject repeated at least 3 out of 5 or 2 out of 3 keywords correctly. Sentences were roving at 65, 70 or 75 dB sound pressure level (SPL) with an initial signal-to-noise ratio (SNR) of +20 dB. When a sentence was scored correct, the SNR of the next sentence was reduced. When a sentence was scored incorrect, the SNR of the next sentence was increased. In the first phase, the SNR was reduced or increased in 10 dB steps following a correct or incorrect response. In phase two and three, steps of 5 and 2.5 dB were used. Progression from phase 1 to 2 and phase 2 to 3 took place whenever a reversal occurred, for example when 2 sentences scored correct were followed by a sentence scored incorrect. The average SNR of the last 16 sentences, all in phase 3, was calculated, which resulted in the SRTn. A cut-off of 30dB was used, as a higher score was considered a situation with virtually no noise. Patients could adjust the speech processor programs to their preference, therefore microphone settings may differ between patients. Since this was no variable of interest, no data concerning microphone settings was gathered. Loudness balancing was done prior in a clinical setting and patients were asked to balance volume between both CIs.

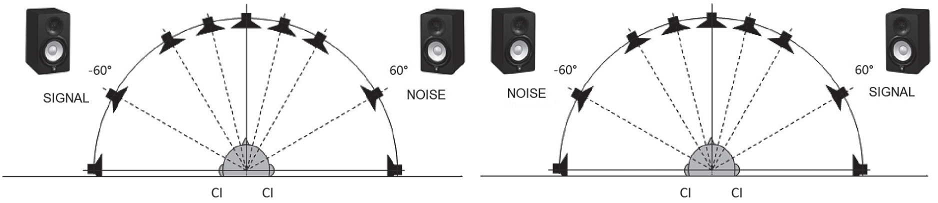

Figure 1 | Measuring the squelch effect in the SISSS.

The SISSS was performed with a. speech from the left and noise from the right (S-60N+60) and b. vice versa (S+60N-60) while using the left, right, and both CIs. The best performing ear was determined by the best bilateral score with speech from the left (S-60 N+60) or the right (S+60N-60). CIs indicates cochlear implants; SISSS, speech intelligibility-in- noise with spatially separated sources.

Main outcome measure

The main outcome measure of the current prospective study was the squelch effect. To calculate a squelch effect, the SISSS was evaluated in both the bilateral and unilateral condition (by turning the CI off at the side of the noise). By comparing these conditions, the additional effect of the second CI was calculated. The sequence of measurement was structurally equal: first the bilateral condition, then the unilateral conditions, starting with CI1 followed by CI2. The condition with speech from the left and noise from the right (S-60 N+60) was tested first followed by the condition in which speech and noise were reversed (S+60 N-60).

When sounds come from different directions, patients usually have a best performing side. To establish a patient's best performing ear, we determined the ear with the best score in the bilateral situation when speech came either from left or right. For example, if a patient's best SRTn was when speech came from the left and noise from the right (S-60 N+60), this patient's best performing side was left.[30]

Statistical analyses

Before analyzing the data, data were double-checked by two independent persons without connections to the Utrecht otorhinolaryngology department. None of the scores were normally distributed, thus we reported medians and interquartile ranges except for baseline characteristics, which were normally distributed. The squelch effect was derived from the data multiple times: for both ears separately and for the patient's best performing ear only. To compare the bilateral and unilateral results, the Wilcoxon signed rank test was used. To compare the outcomes between years of follow-up, the Friedman and Wilcoxon signed rank test were used. To compare the proportions of patients with a squelch effect during follow-up, a Fisher's Exact Test was used. We recalculated the proportions using a minimum difference of 1SD of the normal hearing people SISSS results to only include the patients that exhibit a clinically relevant squelch effect, which was 2.0dB for S+60 N-60; 1.7 dB for S-60 N+60 and 1.8 dB for the best performing ear.[30] Data were presented including and excluding patient 19's 3 year follow-up results because of nonuse of his right CI due to pain complaints. SPSS version 21.0.0 for Windows was used and a *p* value <0.05 was considered statistically significant.

RESULTS

Participants were included between December 2009 and September 2012. The baseline characteristics of these patients are reported in Table 1. One patient was diagnosed with Kahler's disease a few weeks after inclusion and was therefore replaced by another patient. No patients were lost to follow-up during the 3-year follow-up. As mentioned above, due to pain at the right implant site, one patient did not wear his right CI several months prior to the 3rd year evaluation. In the analyses, this patient's 3-year follow-up results are shown in the data and interpreted separately.

Table 1 | Patient characteristics

	n=19
Gender male:female	8:11
Age at CI (years)	47.8 (15.9) [18-70]
Age start severe hearing loss AD (years)	30.5 (17.2) [3-63]
Age start severe hearing loss AS (years)	30.0 (17.5) [3-63]
PTA AD (dB)	106 (16) [80-130]
PTA AS (dB)	108 (18) [77-130]
Maximum phoneme score (%)	42.1 (27.6) [0-90]
Treatment hospital	
Utrecht	8
Maastricht	5
Nijmegen	3

Table 1 | Continued

	n=19
Treatment hospital	
Leiden	2
Groningen	1
HA use before CI	
Yes	15
No	4
Cause of deafness	
Hereditary	9
Unknown and progressive	6
Sudden Deafness	2
Head trauma	1
Sound exposure	1

Mean (standard deviation) [range]; CI indicates cochlear implantation; HA, hearing aid; PTA = pure tone audiometry (average of 500, 1000 and 2000 Hz).

Main outcome measure – squelch effect

Left and right ear

Figure 2 depicts boxplots of the median SRTn in the bilateral and the unilateral conditions for the left and right ear separately during a 3-year follow-up. Median scores after 1 and 2 year did not differ between both conditions. After 3 years, a significant squelch effect for the left ear was observed. The median SRTn was 4.4dB [0.3 – 9.1] in the bilateral situation and 5.0dB [1.6 – 8.4] in the unilateral situation (*P*=.038). Figure 3 depicts the absolute squelch effect for the left and right ear separately, accompanied by the 10th and 90th percentile lines. When looking at the data for the right ear, Figure 3, depicting the absolute squelch effect for both ears during follow-up, clearly shows that the bilateral SRTn of patient 19 clearly deteriorated due to nonuse of his right CI over time. This score from the S+60 N-60 configuration is an outlier in comparison to the other scores and this patient's previous scores. After excluding this patient from this analysis, a squelch effect on group level was present: bilateral SRTn: 2.7dB [-1.7 – 7.6] and unilateral SRTn: 4.3 [-0.9 – 6.9] (*p*=.045).

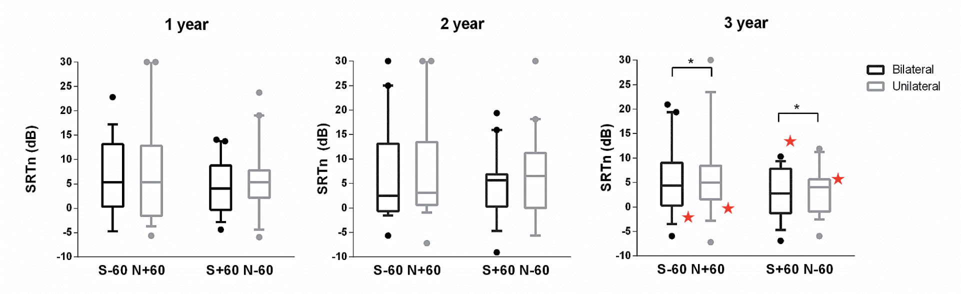

Figure 2 | Boxplot of bilateral and unilateral scores in both ears during a 3-year follow-up.

The red asterisks indicate patient 19's results who did not wear his right CI before the 3rd year evaluation. The worsening of the bilateral score when speech came from the right indicates the deterioration of right side hearing. Without this patient, a squelch effect was present for the left and right ear on group level. With this patient, however, this was not significant for the right ear anymore. S-60N+60 indicates speech from 60 degrees azimuth to the left and noise from 60 degrees azimuth to the right, S+60N-60 vice versa. The median is marked by the horizontal line in the boxes; the 25th and 75th percentiles are marked by the ends of the boxes; the 10th and 90th percentiles are marked by the whiskers; the outliers are displayed by the filled circles; * Wilcoxon signed rank test p<0.05.

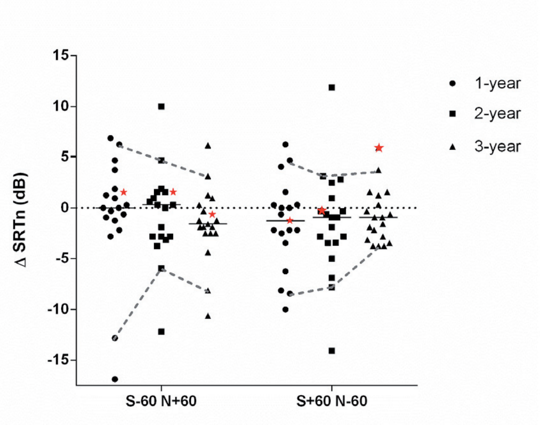

Figure 3 | Squelch effect for the left (S-60N+60) and right ears (S+60N-60).

The difference (bilateral – unilateral scores) for the left and right ears during 3 years of follow-up. A score below zero portrays a squelch effect. The median value is indicated with the horizontal line. The 10th and 90th percentiles are depicted with a gray dashed line. The red asterisks point out the scores of patient 19. This figure shows his deterioration of bilateral integration of sounds when speech comes from the right and noise from the left after 3 years of follow-up.

The proportion of patients that demonstrated a squelch effect in the left ear was 8/19 (42%) after 1 year, 8/19 (42%) after 2 years, and 13/18 (72%) after 3 years (excluding patient 19). When applying a minimum difference of 1.7 dB between both conditions, the proportions were 4/19 (21%) after 1 year, 8/19 (42%) after 2 years, and 9/18 (50%) after 3 years.

The proportion of patients that demonstrated a squelch effect in the right ear was 11/19 (58%) after 1 year, 14/19 (74%) after 2 years, and 13/18 (72%) after 3 years (excluding patient 19). When applying a minimum difference of 2.0 dB, the proportions were 9/19 (47%) after 1 year, 8/19 (42%) after 2 years, and 7/18 (39%) after 3 years.

Best performing ear

Figure 4 shows boxplots of the median SRTn in the bilateral and the unilateral condition for our patient's best performing ear during a 3-year follow-up. After 1 year, no difference between both conditions was objectified. After 2 years, there was a significant difference between the bilateral SRTn (2.5 dB [-0.6 – 6.9]) compared with the unilateral SRTn (2.5 dB [0.3 – 11.3]) (*p*=.035). After 3 years, the squelch effect was larger with a bilateral SRTn of 0.6 dB [-3.1 – 7.5] compared with a unilateral SRTn of 2.2 dB [-0.9 – 6.9] (this analysis included patient 19, since patient 19's best performing ear was his left ear, *p*=.006).

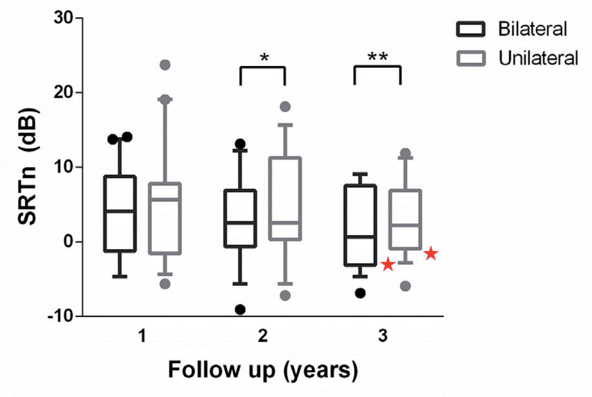

Figure 4 | Boxplot of squelch effect in the best performing ear during a 3-year follow-up

After 2 and 3 years, a squelch effect was present for patients' best performing ear. The red asterisks point out the scores from patient 19's left ear. The median is marked by the horizontal line in the boxes; the 25th and 75th percentiles are marked by the ends of the boxes; the 10th and 90th percentiles are marked by the whiskers; the outliers are displayed by the filled circles; * Wilcoxon signed rank test p<0.05

The proportion of patients that demonstrated a squelch effect in the best performing ear was 13/19 (68%) after 1 year, 12/19 (63%) after 2 years, and 16/19 (84%) after 3 years. After applying a minimum difference of 1.8 dB, the proportions were 8/19 (42%) after 1 year, 9/19 (47%) after 2 years, and 10/19 (53%) after 3 years.

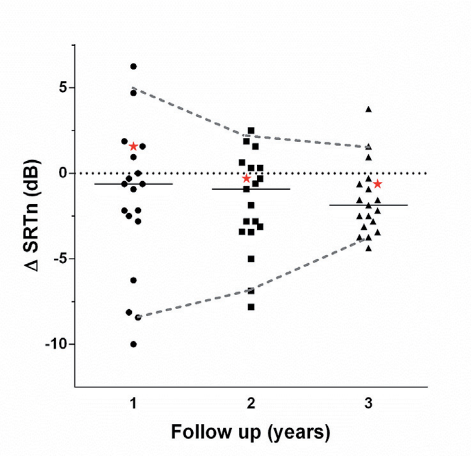

Figure 5 | Squelch effect for the best performing ear.

The difference (bilateral – unilateral scores) for the best performing ear during 3 years of follow-up. A score below zero portrays a squelch effect. The median value is indicated with the horizontal line. The 10th and 90th percentiles are depicted with a grey dashed line. The variation decreases evidently during follow-up. After 3 years, only 3 patients have a positive difference score. The red asterisks point out patient 19's best performing ear results.

Comparing follow-up years

As Figure 3, Figure 5 shows the absolute squelch effect: an advantage associated with bilateral listening as compared with the shadowed ear alone in case the signal and masker are presented from different locations in the horizontal plane. In these figures, the 10th and 90th percentile lines are depicted. What is striking, especially in Figure 5, is the narrowing of variation of scores as time progresses, which results in the significance of the squelch effect on group level. This development indicates that patients exhibit a different development of their hearing abilities with two CIs.

DISCUSSION

Synopsis of study results

In this study we investigated the presence of a squelch effect in a prospective study of simultaneously bilaterally implanted postlingually deafened adults during a 3-year follow-up. In 13 individual patients, a squelch effect was already present in at least one ear after 1 year. On group level, a squelch effect was present in a patient's best performing ear after 2 and 3 years. We found a squelch effect in the left and right ear after 3 years.

Comparison to the existing literature

In literature concerning the squelch effect in bilateral CI users, follow-up ranges from 6 months to 4 years.[24,28] Generally, a squelch effect on group level was seen in studies with at least 1 year of follow-up.[17,27,28] Six months after implantation, a squelch effect was generally not seen or only in individual patients[21,24,26] An increasing squelch effect was seen in a study by Eapen et al. during a 4-year follow-up, indicating that the squelch effect advanced with greater listening experience.[28] Similar to previous studies, we observed a squelch effect in individual subjects after 1 year, but on group level only after 2 years which became more robust after 3 years.

Van Hoesel stated that binaural unmasking benefits for bilateral CI patients are generally minimal.[16] Gifford et al. found a squelch effect for the 1st and 2nd implanted ear of 0.9dB and 2.3 dB in a group of 30 bilaterally implanted patients, of which four were implanted simultaneously.[11] Another study found a squelch effect of 0-2 dB with a single interfering noise.[8] In our study, we found a squelch effect in the amount of 0.6 dB after 1 year (not significant), 0.9 dB (significant) and 1.9 dB after 3 years (significant) for the best performing ear. After 3 years, the squelch effect amounted to 1.7 dB in the left ear and 1.3 dB in the right ear. These numbers are in accordance with previous studies.

Our results suggest a development and increase of the squelch effect in the years following bilateral cochlear implantation. This effect implies that the brain is able to integrate different cues of sound to segregate sound from noise.[28] Better separation of sound from noise improves hearing in noise in bilateral CI users. The increase in the squelch effect suggests that binaural processing continue to adapt in the years following bilateral cochlear implantation.

Strengths and weaknesses of this study

A major strength of this study is that we investigated a homogeneous group of patients because we used fixed inclusion criteria: only simultaneously bilaterally implanted patients were included. A second strength is the lack of loss to follow-up, allowing comparison across years. A third strength is the use of variable SNRs instead of a fixed SNR which would have led to ceiling effects.[24] A limitation of our study is that we did not control for binaural summation effects. Because binaural hearing is based on three principles, overlap in the effects is inevitable. By testing patients bilaterally and unilaterally with one CI switched off, a difference in loudness arises. Summation could have amplified the binaural squelch effect. However, summation causes louder speech and noise, therefore we think that the impact of this potential weakness is limited. In order to compensate for this limitation, patients were instructed to adjust the volume of their CI to the preferred level in the unilateral situation. Another limitation is that we did not control for different microphone settings among patients.

Future research

In the future, we will evaluate the development of a squelch effect in the group of sequentially implanted bilateral CI users after at least 2 years of follow-up.

CONCLUSION

This study shows that patients who underwent simultaneous bilateral cochlear implantation developed a measurable benefit from the squelch effect after 2 years in their best performing ear and after 3 years in both ears separately. This effect increased over time. These observations suggest that the brain uses interaural differences to segregate sound from noise after simultaneous bilateral cochlear implantation. The growth of the squelch effect over time suggests cortical integration and differentiation of inputs from bilateral CIs due to continued binaural processes beyond the first years after implantation.

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Chapter 6

No Squelch Effect After Sequential Bilateral Cochlear Implantation in Postlingually Deafened Adults: Is There a First Ear Advantage?

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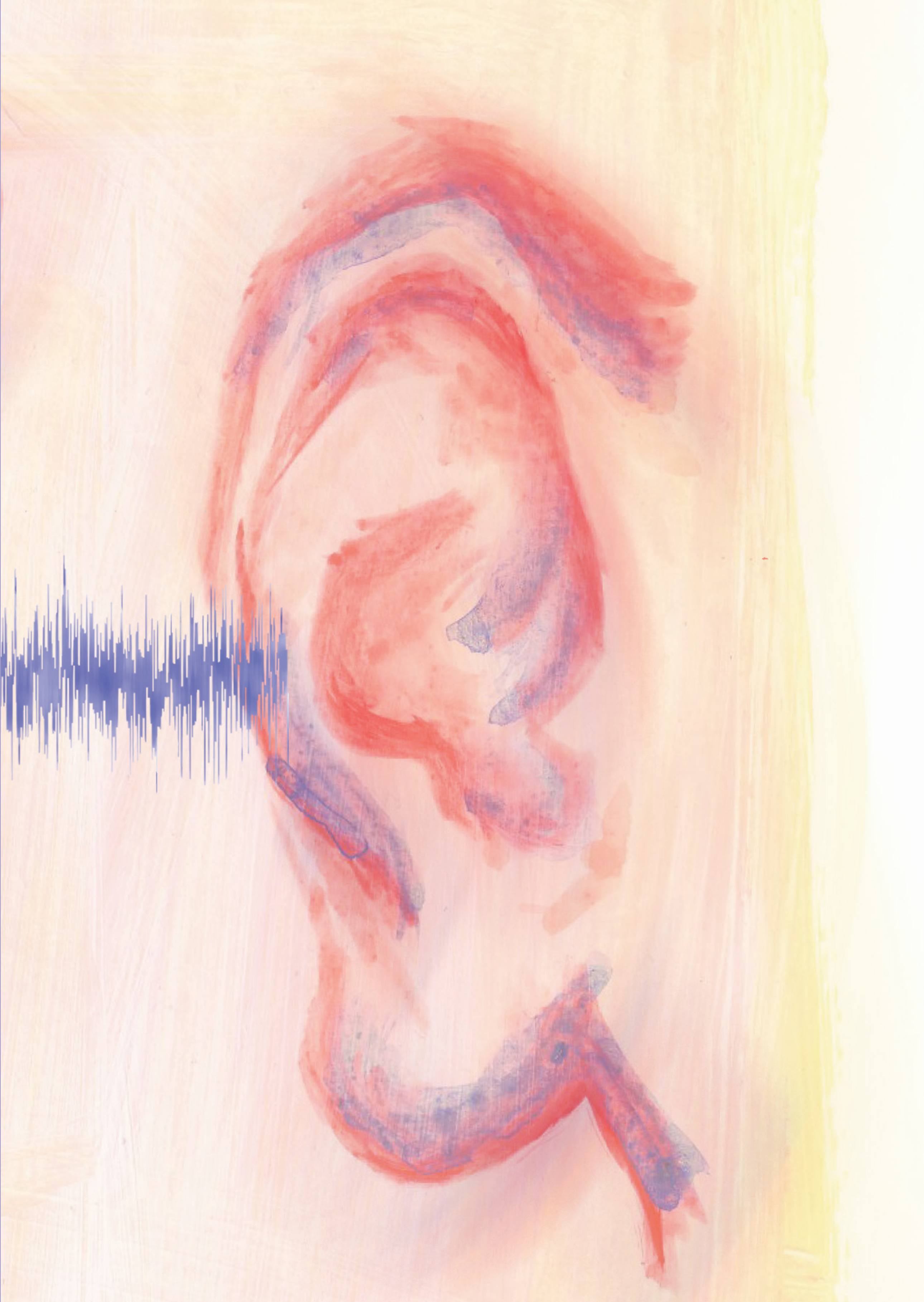

ABSTRACT

Objectives: To investigate whether a squelch effect develops in postlingually deafened adults after sequential bilateral cochlear implantation.

Study design: Prospective study as part of a randomized controlled trial on the difference between simultaneous versus sequential bilateral cochlear implantation.

Setting: Tertiary referral center.

Participants: Sixteen postlingually deafened adults.

Intervention: Sequential bilateral cochlear implantation with a 2 year inter-implant interval.

Main outcome measure: A squelch effect was defined as a better bilateral score than unilateral score on a speech-intelligibility-in-noise test with spatially separated sources. The squelch effect was evaluated for the participants' best performing CI ear, the left CI in the condition with speech from -60 degrees azimuth and noise from +60 degrees azimuth (S-60 N+60), the right CI (N-60 S+60), CI1 and CI2. Evaluations took place 1, 2 and median 4 years after sequential implantation.

Results: No significant squelch effect was found, except for the right CI (N-60 S+60) after 2 years. No differences in speech perception-in-noise from straight ahead were seen between CI1 and CI2. Comparing performance of participants whose better or worse ear was implanted first did not reveal differences either. For the best performing situation, 7/16, 6/16 and 3/12 participants exhibited a squelch effect after 1, 2 and 4 years of follow-up.

Conclusions: Participants who underwent sequential bilateral cochlear implantation with a 2 year inter-implant interval did not develop an evident squelch effect on group level after a median follow-up of 4 years. Individual participants were able to make use of the squelch effect. The less evident squelch effect is at odds with our group of simultaneously implanted bilateral cochlear implant users. Neither a difference between CI1 and CI2, nor implanting the better or worse ear first could explain the less evident squelch effect in these patients.

Trial Registration: Dutch Trial Register NTR1722

Key Words: cochlear implants, sequential bilateral cochlear implantation, sensorineural hearing loss, deafness, squelch effect, binaural hearing, spatial hearing, speech in noise

Level of evidence: 1b

INTRODUCTION

Over the last decades, the advantages of bilateral cochlear implantation (BiCI) over unilateral cochlear implantation (UCI) in patients with severe-to-profound sensorineural hearing loss (SNHL) have been investigated extensively, revealing a benefit in speech perception in noisy surroundings and localization abilities.[1,2] The advantages of BiCI are based on three binaural hearing effects: the head shadow effect, the binaural summation effect, and the squelch effect.[3] The squelch effect is manifest in situations with spatially separated speech and competing noise. Squelch is the ability of the auditory system to combine the information from two ears centrally and segregate speech from noise by differences in timing and amplitude of sounds between both ears. This way, speech perception in noise is improved.[3]

In one of our previous articles[3], a literature overview on the squelch effect in bilateral cochlear implant (CI) users was provided. To summarize, in these studies on the squelch effect in bilateral CI users, study population existed often of a mix of simultaneously and sequentially implanted patients with varying follow-up and test set-ups. Most of these studies showed benefits of the head shadow and binaural summation effects, yet limited evidence for the squelch effect in CI users was found.[3]

As part of a randomized controlled trial on the difference between simultaneous BiCI (simBiCI) versus sequential BiCI (seqBiCI), our research group previously presented data on the squelch effect in 19 patients after simBiCI with a 3 year follow-up.[3] These participants developed a squelch effect three years after simBiCI for both the left and right CI ear. Moreover, for the participants' best performing side a squelch effect was already evident two years after simBiCI.[3] The median squelch effect amounted to 1.9 dB in the best performing side.

Patients that receive one CI and later receive a second CI (seqBiCI), accustom to hearing with one CI for two years. After receiving the second CI, they accustom to hearing with two CIs. Compared to simBiCI, the delay in bilateral CI use may require further adjustment. The development of a squelch effect may therefore be different for patients following seqBiCI compared with simBiCI. In the current prospective study, we investigated the development of a squelch effect in a homogeneous group of seqBiCI participants using a set-up that is sensitive to detect a squelch effect and a fixed interimplant interval of 2 years, which distinguishes this study from previous studies. In brief, the aim of this study is to evaluate whether a squelch effect develops in postlingually deafened adults following seqBiCI.

MATERIAL AND METHODS

Ethical considerations

This study was approved by the Medical Ethics Committees of all participating centers (UMC Utrecht, Maastricht, Nijmegen, Leiden and Groningen) (NL2466001808), registered in the Dutch Trial Register (NTR1722) and conducted according to the Declaration of Helsinki.

Study design and participants

This study is embedded in a multicenter randomized controlled trial (RCT) on the difference between simBiCI versus seqBiCI in adults with severe-to-profound postlingual SNHL.[1,2,4] In the current study we focused on participants following seqBiCI with a 2 year inter-implant interval who, by initial protocol, were evaluated 1 and 2 years following seqBiCI. Thus, evaluation took place 1 and 2 years after bilateral implantation. An additional evaluation was performed cross-sectionally between August 2017 and September 2017, resulting in a median 4 [interquartile range (IQR):3.3 - 5.0] years after seqBiCI. All participants were implanted with Advanced Bionics HiRes90K® CIs and were fitted with Harmony speech processors.

Hearing evaluation

Test set-up and procedure

Speech intelligibility-in-noise with spatially separated sources (SISSS) was tested using a set-up[5] in which sentences were presented horizontally from 60° to the left (-60° azimuth) or right (+60° azimuth) of the subject and speech-spectrum-shaped noise was presented from the opposite side simultaneously. Thirty sentences were presented at roving sound pressure levels (60, 65 or 70 dB) with an initial signal-to-noise ratio (SNR) of +20 dB. Following a correct (2/3 or 4/5 key words repeated correctly) or incorrect response the SNR was reduced or increased, respectively. The test comprised three phases. Following a correct or incorrect response, in phase 1 the SNR was altered in 10 dB steps. In phase 2 and 3, the SNR was altered with 5 and 2.5 dB steps. Progression from one phase to another occurred whenever a reversal from a correct to an incorrect response or vice versa took place. The speech reception threshold in noise (SRTn) was calculated by averaging the SNR of the last 16 sentences, all in phase 3.

The sequence of measurements was structurally equal: first the bilateral condition, then the unilateral conditions, starting with the first CI (CI1) followed by the second CI (CI2). Speech from -60° and noise from +60° (S-60 N+60) was tested first, followed by noise from -60° and speech from +60° (N-60 S+60). Participants could adjust the speech processor programs to their preference. Right to left loudness balancing with equal volume control settings was done prior in a clinical setting and participants were asked to balance volume between both CIs prior to the measurements.

Main outcome measure

The primary outcome measure was a squelch effect: a better SRTn in the bilateral condition than the SRTn in the unilateral condition with the CI at the noise side switched off.[3] The squelch effect was assessed multiple times: for the left CI (in the condition S-60 N+60), the right CI (N-60 S+60), CI1, CI2 and for the participant's *best performing side* only; when sounds come from different directions, participants usually have a *best performing side*. To establish a participant's best performing side, we determined the ear with the best score in the bilateral situation for S-60 N+60 and S+60 N-60[1,2,4] The best performing side was left if the first condition shows the better result or right if the second condition shows the better result.

Statistical analyses

Before analyzing the data, data were double-checked by two independent researchers. Data were presented as counts, percentages and medians with [IQRs] since most of the results were not normally distributed. To compare the bilateral versus unilateral SRTn and the unilateral scores of CI1 versus CI2, the Wilcoxon signed-rank test was used. The median difference was calculated using the Hodges-Lehman estimate. Proportions of participants developing a squelch effect were calculated using a minimum difference between bilateral and unilateral SRTn of 1 SD based on the validation analyses of the test set-up with normal hearing subjects, which was 1.8 dB for the best performing side.[3,5] A minimum difference was applied to make sure to detect a clinically relevant squelch effect and not a pseudo effect based on test-retest variability. SPSS version 22.0 was used and a *p*-value <.05 was considered statistically significant.

RESULTS

Baseline characteristics

Nineteen participants were included in the study and randomly allocated to the seqBiCI group between December 2009 and August 2012. Three participants did not proceed to seqBiCI after the first CI and were lost to follow-up, resulting in 16 participants. Of these 16 participants, eleven were male and the median age at inclusion was 60 years [45 – 65]. The median duration of deafness was 18 years [8 – 35] for the left ear and 16 years [8 – 33] for the right ear. Etiology of deafness was hereditary (7), unknown and progressive (7) and meningitis (2). Preimplantation median pure-tone average for the frequencies 0.5 through

4 kHz was 109 dB [93 – 115] for the left ear and 99 dB [92 – 108] for the right ear. The median maximum CVC phoneme score was 42% [30 – 55] preimplantation. All participants used hearing aids (HAs) preimplantation.

After inclusion, participants chose the ear to be implanted first. Both ears met the inclusion criteria for implantation. As shown in Table 1, duration of severe-to-profound SNHL and PTA did not differ between CI1 and CI2. Furthermore, the preimplantation better ear was determined by (1) asking participants and (2) comparing bilaterally aided speech audiograms. Both approaches resulted in comparable results: in 13/16 participants, the self-reported better ear corresponded with the better ear determined by speech audiometry. In 1 participant speech audiometry did not favor one ear over the other. In the majority of participants (12/15), CI1 was the self-reported worse performing ear, whereas in 3/15 participants, CI1 was the self-reported better performing ear preimplantation.

Table 1 | Baseline differences between CI1 ear and CI2 ear

	CI1	**CI2**
Preimplantation		
Duration of severe to profound SNHL (years)	18 [9 – 35]	18 [9 – 35]
PTA (dB)	104 [93 – 115]	99 [92 – 109]
Pure tone threshold at 500Hz	90 [80 – 101]	90 [75 – 95]
Pure tone threshold at 1000Hz	100 [90 – 110]	95 [85 – 110]
Pure tone threshold at 2000Hz	110 [95 – 120]	108 [90 – 120]
Pure tone threshold at 4000Hz	117 [104 – 130]	118 [99 – 130]
Preimplantation better ear (CI1=CI2, n=1)		
Self-reported	3/15	12/15
Speech audiometry	3/15	12/15
Postimplantation		
Right ear implanted	5/16	11/16
Contralateral hearing aid use		
Year 1	10/16	Not applicable
Year 2	11/16	Not applicable

Scores are presented as median values [interquartile range] or counts; PTA: pure-tone average.

Follow-up

As previously mentioned, these 16 participants were evaluated after 1 and 2 years of bilateral CI use. Twelve participants were willing and able to participate in an additional evaluation that took place after a median 4.0 years [3.3 - 5.0] of bilateral CI use. In five of these 12 participants the Harmony speech processors had been replaced with Naída speech processors before this evaluation.

Squelch effect

As shown in Table 2, no significant differences between the bilateral and unilateral conditions were seen for the best performing side nor the left and right CI ear except for the right CI ear (N-60 S+60) after 2 years of follow-up: bilateral SRTn: 5.2 dB [0.5 – 10.3] versus unilateral SRTn: 5.2 dB [1.3 – 14.8], *p*=.038. Figure 1 depicts boxplots of the SRTn in the bilateral and unilateral conditions for our participant's best performing side. No significant differences were seen between the bilateral and unilateral SRTn for the participants' best performing side during all years of follow-up.

Table 2 | Difference between bilateral and unilateral scores in the sequential BiCI group (n=16)

	Bilateral SRTn Median dB (IQR)	Unilateral SRTn median dB (IQR)	Difference[a] (95% CI)	*P* value[b]
Best performing situation				
Year 1	2.7 [0.1 – 7.8]	5.2 [-0.9 – 9.9]	0.7 [-2.0 – 2.7]	.776
Year 2	2.0 [-0.3 – 6.5]	2.0 [-2.1 – 5.0]	0.3 [-1.3 – 2.2]	.691
Year 4 (n=12)	2.3 [0.6 – 5.2]	2.3 [-0.1 – 4.3]	-0.2 [-2.0 – 2.7]	.790
Left CI (S-60 N+60)				
Year 1	4.5 [0.2 – 8.7]	5.9 [0.8 – 10.2]	0.5 [-2.0 – 3.1]	.856
Year 2	3.6 [1.8 – 8.3]	3.3 [-0.9 – 7.0]	-0.4 [-2.2 – 1.7]	.532
Year 4 (n=12)	4.5 [1.8 – 7.5]	4.2 [3.8 – 5.2]	0.5 [-1.7 – 3.8]	.638
Right CI (N-60 S+60)				
Year 1	6.4 [2.6 – 8.8]	6.9 [1.9 – 10.4]	0.3 [-1.6 – 2.2]	.776
Year 2	5.2 [0.5 – 10.3]	5.2 [1.3 – 14.8]	1.1 [0.2 – 3.3]	.038*
Year 4 (n=12)	5.9 [1.6 – 10.3]	4.8 [0.7 – 18.1]	1.4 [-1.9 – 5.5]	.285
CI1				
Year 1	4.5 [0.2 – 8.8]	5.2 [0.7 – 7.3]	-0.8 [-3.0 – 1.4]	.277
Year 2	3.6 [0.9 – 9.3]	3.8 [-0.9 – 9.8]	-0.3 [-1.7 – 1.9]	.513
Year 4 (n=12)	5.8 [2.7 – 8.6]	4.7 [1.4 – 16.9]	1.7 [-1.9 – 5.6]	.347
CI2				
Year 1	6.9 [3.6 – 10.7]	8.3 [2.4 – 12.0]	1.5 [-2.5 – 5.3]	.423
Year 2	4.5 [0.9 – 9.2]	4.5 [1.4 – 15.4]	0.6 [-0.3 – 4.1]	.222
Year 4 (n=12)	4.8 [0.7 – 6.4]	4.2 [0.9 – 6.9]	0.4 [-1.4 – 4.2]	.722

a: The median difference was calculated using the Hodges-Lehman estimate; b: Bilateral and unilateral SRTn were compared using the Wilcoxon Signed Rank test for related samples. SRTn: speech reception threshold in noise; IQR=interquartile range; CI=confidence interval; *= *p*-value<.05; S-60 N+60: speech perception-in-noise test with speech from -60 degrees azimuth and noise from +60 degrees azimuth resulting in a speech reception threshold in noise expressed in decibels; N-60 S+60: speech and noise reversed; CI1: first implanted cochlear implant; CI2: second implanted cochlear implant.

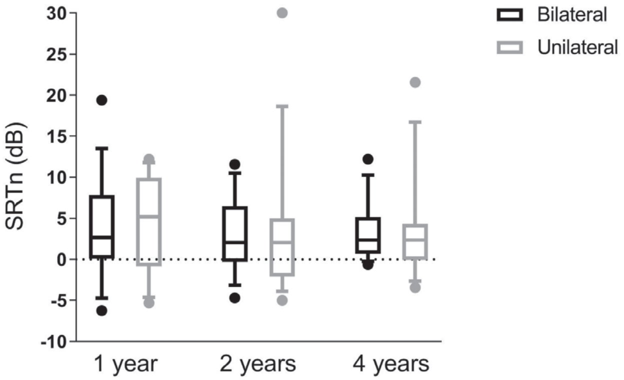

Figure 1 | Boxplot of the speech reception threshold in noise for the best performing ear during a 4-year follow-up.

The median, marked by the horizontal line in the box; the 25th and 75th percentiles, marked by the ends of the box; the 10th and 90th percentiles, marked by the whiskers; and the outliers, displayed by the filled circles, are depicted. As there are no significant differences between the unilateral and bilateral condition, no squelch effect is shown.

The proportions of participants demonstrating a squelch effect for the best performing ear, the left CI, the right CI, CI1 and CI2 after applying a minimum difference of 1.8 dB[3,5] are reported in Table 3. No more than 50% of participants exhibit a squelch effect in any of the conditions.

Table 3 | Proportions of participants that exhibited a squelch effect taking into account a minimum difference (1.8 dB) (n=16)

	Year 1	Year 2	Year 4 (n=12)
Best performing situation	7/16 (44%)	6/16 (38%)	3/12 (25%)
Left CI (S-60 N+60)	7/16 (44%)	5/16 (31%)	5/12 (42%)
Right CI (N-60 S+60)	5/16 (31%)	6/16 (38%)	4/12 (33%)
CI1	4/16 (25%)	6/16 (38%)	6/12 (50%)
CI2	8/16 (50%)	5/16 (31%)	3/12 (25%)

S-60 N+60: speech perception-in-noise test with speech from -60 degrees azimuth and noise from +60 degrees azimuth resulting in a speech reception threshold in noise expressed in decibels; N-60 S+60: speech and noise reversed; CI1: first implanted cochlear implant; CI2: second implanted cochlear implant.

Figure 2 depicts individual data of the absolute squelch effect (difference between unilateral and bilateral score) for the best performing situation, accompanied by the 10th and 90th percentile lines. For all years of follow-up the group median is not below zero, indicating no median squelch effect. Furthermore, large variation exists between participants and this variation does not decrease over time. As a comparison, the difference scores of 19 simultaneously implanted bilateral CI users were added to the figure.[3,4] In this group, we found a squelch effect on group level after three years of follow-up for the left and right CI side and already after two years of follow-up for their best performing side. A distinct decrease in inter-individual variability is seen in the simBiCI group over time, which is not seen in the seqBiCI group. Furthermore, equal to lower proportions of participants demonstrating a squelch effect were seen in the seqBiCI group compared to the simBiCI group.

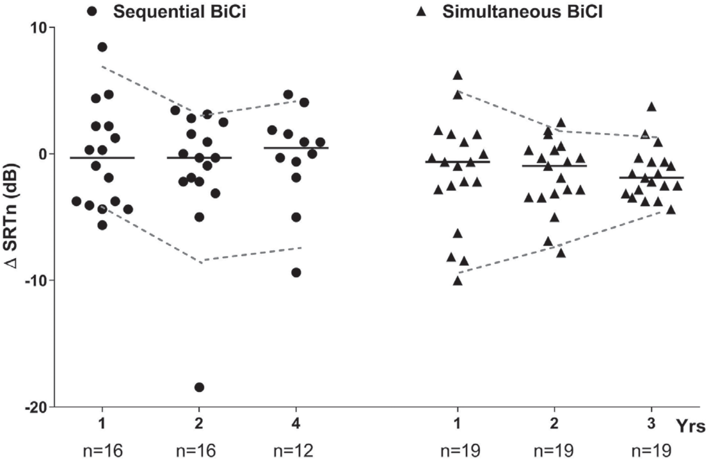

Figure 2 | Squelch effect for the best performing ear in our sequential (rounds) compared to our simultaneous (triangles) BiCI group.

The difference (bilateral – unilateral scores) for the best performing ear during a 4-year follow-up are presented. A score below zero depicts a squelch effect. The median value is depicted with a *horizontal* line. The 10th and 90th percentiles are depicted with a *gray dashed* line. BiCI indicates bilateral cochlear implantation.

Performance of first and second CI

In order to explain the less evident squelch effect after seqBiCI, performance of the first and second CI on a speech perception-in-noise from straight ahead test was compared using the Wilcoxon signed-rank test. We hypothesized that the inter-implant interval of 2 years may have caused an unbeatable advantage in favor of CI1. As shown in Table 4, no significant difference in speech perception-in-noise from straight ahead between CI1 and CI2 was seen. However, this may be due to the low sample size and the great variability between participants. Subjectively, the researchers performing the evaluations noticed that participants tended to preference their CI1 ear, which was sometimes strikingly called “the listening ear”. The results shown in Table 4 however did not support this subjective observation.

Table 4 | Differences in speech perception-in-noise from straight ahead between CI1 and CI2 in the sequential BiCI group

	CI1 median (IQR)	**CI2** median (IQR)	**Difference** (95% CI)	***P* value**
S0N0 (dB)				
Year 1 (N=16)	10.0 [6.8 – 12.6]	10.6 [8.4 – 15.0]	1.7 [0.0 – 3.8]	.057
Year 2 (N=16)	9.1 [7.0 – 13.8]	10.0 [8.1 – 22.0]	2.7 [-0.9 – 7.7]	.205
Year 4 (N=12)	11.9 [8.5 – 16.5]	12.0 [6.0 – 15.7]	-1.4 [-4.2 – 4.8]	.480

S0N0: speech perception-in-noise test with speech and noise from straight ahead resulting in a speech reception threshold in noise, expressed in decibels; IQR=interquartile range; CI=confidence interval.

Implanting the better or worse ear first

To further explore the less evident squelch effect after seqBiCI, a second, partly overlapping, comparison was made, namely the difference between implanting the better or worse ear first. Most participants, although they suffered from bilateral severe-to-profound SNHL, subjectively had a 'better' ear preimplantation. As stated earlier, to determine the better ear preimplantation, we (1) asked participants what their better ear preimplantation was and (2) checked preimplantation aided speech audiograms. Both approaches resulted in comparable results: in 13/16 participants, the self-reported better ear corresponded with the better ear determined by speech audiometry. In one participant speech audiometry did not favor one ear over the other. The poorer preimplantation ear was implanted first in 12/15 participants. In 3/15 participants the better preimplantation ear was implanted first. All 16 participants used HAs before receiving CI1, of which they received limited to no benefit. We calculated the proportions of participants that developed a squelch effect for both groups after BiCI for the conditions with speech to the better ear and noise to the worse ear and vice versa. No large differences were seen between participants whose better or worse ear was implanted first and, since sample size was small, no analyses could be performed.

DISCUSSION

Key findings

In this study we investigated the development of a squelch effect in postlingually deafened adults after seqBiCI with an inter-implant interval of 2 years. Except for the right CI ear after 2 years, no statistically significant squelch effect was evident in the 16 participants after 1 and 2 years, and 12 participants after a median 4 years. For the best performing situation, 7 of 16, 6 of 16 and 3 of 12 participants exhibited a squelch effect after 1, 2 and 4 years of follow-up. These results are at odds with the results we found in our group of simultaneously implanted bilateral CI users who showed a significant squelch effect on group level after 3 years for the left and right CI side and already after 2 years for their best performing side.

We evaluated whether a difference in performance between the first and second CI or a difference between implanting the better or worse ear first could explain this less evident squelch effect. Neither of these comparisons holds as a firm explanation for the less evident squelch effect after seqBiCI compared to simBiCI. Implanting the better ear first does not seem to result in significantly better overall results. Therefore, we did not find evidence to change the current clinical inclination to implant the worse ear first in bilateral cases.[10–12] A clinical advantage of implanting the ear with the least residual hearing first promotes bimodal hearing before receiving CI2, which in turn facilitates a binaural summation effect.[13] In our participants, 10/16 participants still used a contralateral HA after receiving CI1.

Comparison with literature

Other studies have examined the development of a squelch effect in postlingually deafened adults after seqBiCI as well and found variable results. In 21 bilateral CI users with uneven experience with CI2, a squelch effect was seen in the left ear, but not in the right ear.[6] In another study no significant squelch effect was seen for CI1 (26 participants) and for CI2 (18 participants) after 3 or 9 months of bilateral CI use.[7] In a third study, no squelch effect was seen in 29 participants of whom 27 were sequentially implanted with at least 6 months of bilateral experience.[8] Gifford et al. found a mean squelch effect of 0.9 and 2.3 dB for CI1 and CI2 in 30 bilateral CI users, of whom 26 were sequentially implanted. In a sentence recognition test at +5 dB SNR, a mean squelch effect of 6.1 and 7.2 percentage points was found for CI1 and CI2.[9] Yet, the differences between bilateral and unilateral scores were not statistically tested for significance. Large heterogeneity exists between these studies concerning the test set-up (speech from front versus speech from the sides), use of fixed or adaptive SNR, statistical testing of squelch effect and finally study population. To conclude, literature on the squelch effect in patient after seqBiCI is ambiguous. In our previous study[3], a squelch effect developed in the simBiCI group over 2 and 3 years of follow-up. Yet, in the current study, no squelch effect developed in the seqBiCI group in all conditions and follow-up years, except for the N-60 S+60 condition after 2 years of follow-up.

Strengths and limitations

The major strength of our study is that prospectively collected data of a random homogeneous group of sequentially implanted participants were used. The inter-implant interval was set at 2 years for all participants. This is in contrast to most studies analyzing the squelch effect. Furthermore, we were able to compare the results to a random group of simultaneously implanted participants. Another strength is that our test set-up is specifically sensitive to detect a squelch effect rather than a head shadow effect compared to conventional (S+0 N+/-90) set-ups.[3]

A limitation of this study is that the sample size calculation was based on the comparison of two groups of 19 participants on speech perception-in-noise from straight ahead. The sample size may have been insufficient for the analyses in the current study. Yet, since a prior study on the squelch effect in our simBiCI participants revealed significant results, the sample size was considered to be sufficient for the same analyses in our seqBiCI group. Furthermore, since the last follow-up measurement was performed cross-sectionally, follow-up was uneven for the twelve participants evaluated additionally. Five of these twelve participants wore Naída speech processors instead of the originally fitted Harmony speech processors. The difference between these two speech processors was not taken into account in this study and should be the subject of future investigations.

CONCLUSION

This study shows that postlingually deafened adults who underwent seqBiCI with a 2 year inter-implant interval did not develop an evident squelch effect at group level after a median four years of follow-up, which is at odds with our simultaneous BiCI data. Neither a difference between CI1 and CI2, nor implanting the better or worse ear first explained the less evident squelch effect in these sequentially implanted patients.

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Chapter 7

No difference in behavioral and self-reported outcomes for simultaneous and sequential bilateral cochlear implantation: evidence from a multicenter randomized controlled trial

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ABSTRACT

Objective: The primary aim of this study was to longitudinally compare the behavioral and self-reported outcomes of simultaneous bilateral cochlear implantation (simBiCI) and sequential BiCI (seqBiCI) in adults with severe-to-profound postlingual sensorineural hearing loss.

Design: This study is a multicenter randomized controlled trial with a 4-year follow-up period after the first moment of implantation. Participants were allocated by randomization to receive bilateral cochlear implants (CIs) either, simultaneously (simBiCI group) or sequentially with an inter-implant interval of 2 years (UCI/seqBiCI group). All sequential patients where encouraged to use their hearing aid on the non-implanted ear over of the first 2 years. Patients were followed-up on an annual basis. The primary outcome was speech perception in noise coming from a source directly in front of the patient. Other behavioral outcome measures were speech intelligibility-in-noise from spatially separated sources, localization and speech perception in quiet. Self-reported outcome measures encompassed questionnaires on quality of life, quality of hearing and tinnitus. All outcome measures were analyzed longitudinally using a linear or logistic regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type).

Results: Nineteen participants were randomly allocated to the simBiCI group and 19 participants to the UCI/seqBiCI group. Three participants in the UCI/seqBiCI group did not proceed with their second implantation and were therefore unavailable for follow-up. Both study groups performed equally well on speech perception in noise from a source directly in front of the patient longitudinally. During all 4 years of follow-up the UCI/seqBiCI group performed significantly worse compared to the simBiCI group on spatial speech perception in noise in the best performance situation (8.70 dB [3.96 – 13.44], *p*<.001) and localization abilities (largest difference 60 degrees configuration: -44.45% [-52.15 – -36.74], p<.0001). Furthermore, during all years of follow-up, the UCI/seqBiCI group performed significantly worse on quality of hearing and quality of life questionnaires. The years of unilateral CI use were the reason for the inferior results in the UCI/SeqBiCI group. One year after receiving CI2, the UCI/seqBiCI group performance did not statistically differ from the performance of the simBiCI group on all these outcomes.

Furthermore, no longitudinal differences were seen in tinnitus burden prevalence between groups. Finally, the complications that occurred during this trial were infection, dysfunction of CI, facial nerve palsy, tinnitus and vertigo.

Conclusion: This randomized controlled trial on bilaterally severely hearing impaired participants found a significantly worse longitudinal performance of UCI/seqBiCI compared to simBiCI on multiple behavioral and self-reported outcomes regarding speech perception in noise and localization abilities. This difference is associated with the inferior performance of the UCI/seqBiCI participants during the years of unilateral CI use. After receiving the second CI however, the performance of the UCI/seqBiCI group did not significantly differ from the simBiCI group.

Trial Registration: Dutch Trial Register NTR1722

Keywords: cochlear implantation; bilateral; sequential; simultaneous; bimodal; randomized controlled trial; evidence based medicine; speech perception; speech localization; quality of life; quality of hearing; tinnitus; hearing loss; deaf

INTRODUCTION

Binaural hearing enables a person to differentiate a sound of interest from background noise and localize sounds by using various effects of binaural hearing such as: summation, head shadow and squelch effect.[1-4] There is a wealth of scientific evidence advocating the bilateral cochlear implantation (BiCI) over unilateral cochlear implantation (UCI), highlighting that input in both ears instead of one holds evident advantages. In recent years, the difference between BiCI and UCI in adults with severe-to-profound sensorineural hearing loss (SNHL) has been studied thoroughly[5-7] evidencing a benefit of BiCI over UCI on speech perception tasks in noise, localization of sounds abilities and quality of hearing and quality of life improvement. Nonetheless, we believe that a lack of high level concrete evidence such as that derived from a randomized controlled trial (RCT) is much needed to elucidate the BiCI advantage over UCI. Many health care systems such as that in the Netherlands do not reimburse the second cochlear implant in adults due to insufficient proof of societal benefit (cost-utility).

Thus far, there is a lack of overall consensus on whether bilateral cochlear implants should be implanted simultaneously or sequentially. Observational studies have demonstrated advantages of simultaneous BiCI (simBiCI) over UCI as well as sequential BiCI (seqBiCI) over UCI, but no comparative studies exist on the difference between simBiCI versus seqBiCI.

In 2016, our research group published the first results of a RCT comparing outcomes of BiCI to UCI (with or without contralateral hearing aid, e.g. bimodal). It showed conclusive evidence that BiCI patients have superior results over UCI patients on speech perception in noise and localization of sounds using various behavioral and self-reported outcome measures[8,9]. UCI patients in that study received a second CI after 2 years of unilateral CI use, enabling researchers to not only investigate the difference between BiCI and UCI (& bimodal), but also evaluate performances between simultaneous BiCI (simBiCI) and sequential BiCI (UCI/BiCI). The results of this cross-sectional comparison demonstrated comparable performances in both groups for almost all outcome measures after 1 year of BiCI experience[10].

It has been reported that short and long-term performance of CI recipients often varies. To date, investigations evaluating long-term outcomes after simBiCI compared with seqBiCI in adult patients are lacking. In the current paper, we present long-term results of 4 year of follow-up using longitudinal analyses that evaluate behavioral outcomes (speech perception and localization), self-reported outcomes (quality of life (QoL), quality of hearing (QoH) and tinnitus outcomes), as well as complications that occurred during the course of this trial.

MATERIALS AND METHODS

Ethical considerations

This study was approved by the Human Ethics Committees of the Academic Medical Center Amsterdam and consecutively tested for local applicability at all participating centers (University Medical Centers of Utrecht, Maastricht, Nijmegen, Leiden and Groningen) (NL2466001808), registered in the Dutch Trial Register (NTR1722) and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants[8-10].

Study design and participants

This RCT compares behavioral and self-reported outcomes of simBiCI to seqBiCI (UCI/seqBiCI group) in adults with severe-to-profound bilateral postlingual SNHL longitudinally during a 4-year follow-up. Data were reported according to the CONSORT statement[11].

Between December 2009 and September 2012, all adults eligible for cochlear implantation by the clinical teams of University Medical Centers Utrecht, Maastricht, Nijmegen, Groningen and Leiden were assessed for this study's inclusion and exclusion criteria[8-10]. The inclusion criteria were: (1) age: 18-70 years; (2) postlingual onset of SNHL; (3) unaided pure-tone average (PTA, mean of 500, 1000, 2000 Hertz) ≥ 70 dB in both ears; (4) duration of severe-to-profound SNHL <20 years in each ear and a difference in duration of deafness between both ears <10 years; (5) marginal benefit of hearing aids (HAs), defined as an aided consonant vowel consonant (CVC) phoneme score for both ears of ≤50% at 65 dB sound pressure level (SPL); (6) Dutch as native language; (7) willingness and ability to participate in all scheduled procedures; (8) general health allowing general anesthesia for the duration of potential simBiCI; (9) Dutch health insurance coverage; and (10) agreement to be implanted with Advanced Bionics® implants. The exclusion criteria were: (1) previous CI; (2) abnormal cochlear anatomy; and (3) chronic ear infections[8-10].

Intervention

After giving written informed consent and undergoing baseline evaluations, patients were randomly allocated to simBiCI or seqBiCI (UCI/seqBiCI group). It is important to note that in the Netherlands, BiCI is not yet reimbursed in adults. The UCI/seqBiCI group had an inter-implant interval of 2 years (Figure 1). Using a web-based randomization program, a block randomization per center strategy was used to obtain an equal distribution between simBiCI and UCI/seqBiCI groups in all centers[8-10]. All participants received an Advanced Bionics HiRes90K® implant (Advanced Bionics, Sylmar, CA, USA) coupled with a Harmony processor with HiRes/HiRes120 processing strategies. Participants in the UCI/seqBiCI group were encouraged to keep using a contralateral hearing aid in the first 2 years before sequential implantation.

Follow-up

All outcome measures, unless otherwise mentioned below, were evaluated at baseline and after 1, 2, 3, and 4 years of follow-up (Figure 1). The follow up visits lasting approximately 2 – 2.5 h entailed filling respective questionnaires and behavioral testing. Participants and observers were not blinded for the intervention during evaluations due to the nature of the intervention.

Behavioral outcome measures

Behavioral outcomes included speech perception in noise coming from a source directly in front of the patient (speech and noise from a target located in front of the listener at 0 degrees azimuth), speech intelligibility-in-noise from spatially separated sources (SISSS), localization capabilities and speech perception in quiet. All behavioral outcomes were conducted using the AB-York Crescent of Sound set-up, with horizontally placed loudspeakers in a semicircle around the participant[12]. Numbers representing the loudspeaker were shown on monitors below the loudspeakers. In the UCI/seqBiCI group, data were obtained from the 'participant's preferred situation' for the tests conducted before the second implantation. The preferred situation was determined as the situation in which patients performed best, either using the CI (CI1) only or the bimodal condition (CI1 + contralateral HA). In the simBiCI group and for the latter two test moments in the UCI/seqBiCI group, data were gathered from tests performed with both cochlear implants switched on[12,13].

Speech perception in noise

The primary outcome was speech perception in noise coming from a source directly in front of the patient, measured with the Utrecht-Sentence Test with Adaptive Randomized Roving levels. Dutch VU-98 were presented in noise at 65, 70 or 75 dB SPL (randomly selected). The number of keywords correctly repeated per sentence was scored. Sentences were presented with an initial signal-to-noise ratio (SNR) of +20 dB. If a sentence was scored correct (2 of 3 or 3 of 5 keywords correct), the SNR of the next sentence was decreased by increasing the noise level. Contrarily, if a sentence was scored as incorrect, the SNR was increased. The SNR was altered in steps of 10, 5 and 2.5 dB. The mean SNR of the last 10 sentences was calculated, resulting in a speech reception threshold in noise (SRTn)[8,12,13]. A lower score reflects better speech perception. An SRTn of 30 dB was considered speech perception in relative silence and was used as a cut-off point for all scores above 30 dB[13].

In the SISSS, also resulting in an SRTn, sentences were presented from 60° azimuth to the left of the patient and noise from 60° azimuth to the right of the patient (S-60 N+60) and vice versa (S+60 N-60).[13] When sounds come from different directions, participants usually have a *best performance situation (BPS)* and a *worst performance situation (WPS)*. A participant's *BPS* was determined as the situation where speech was presented to the ear with the lowest signal-to-noise ratio (SNR) and noise to the ear with the highest SNR. In a participant's *WPS*, speech and noise originate from the opposite sides. In the UCI/seqBiCI group before CI2, the *BPS* was defined as the situation in which the target speech was presented to the implanted ear and noise to the non-implanted ear[8-10,13].

Localization capabilities

For the localization test, participants were instructed to look at the loudspeaker placed directly in front during the entire procedure. A camera was placed in front of the participant and a deviation of the head of the participant was corrected by the observer. Thirty short phrases ("Hello, what's this?") were presented randomly at 60, 65 or 70 dB SPL from one of the loudspeakers. The results were percentage of correct responses. The test was performed in three localization conditions: 15° angle azimuth between 5 loudspeakers, 30° angle azimuth between 5 loudspeakers and 60° angle azimuth between 3 loudspeakers.[8-10]

Speech perception in quiet

Speech perception in quiet from a loudspeaker in front of the patient was measured using the standard Dutch consonant-vowel-consonant (CVC) test, resulting in a maximum percentage correctly repeated phonemes. This was the only behavioral test which was evaluated at baseline, before randomization.

Self-reported outcome measures

Quality of Life

The QoL questionnaires included the EuroQol five-dimensional questionnaire (EQ-5D), the Health Utilities Index mark 3 (HUI3), a Visual Analogue Scale (VAS) on general health, and the Time Trade-off (TTO)[14-17]. The EQ-5D contains a thermometer indicating general health state and five dimensions of QoL: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The result is a single index value for health status: a utility score ranging from -0.33 to 1.00[14,15,18]. The HUI3 consists of eight elements of health status. The result is a utility score between -0.36 and 1.00[16,18]. The VAS on general health contains a thermometer for general QoL, which results in a utility score between 0 and 1[18]. The TTO is an instrument asking participants whether they are willing to trade expected life years for perfect hearing. The utility is calculated as: utility = (life expectancy – number of years a participant would trade) / life expectancy[8]. This question needs good instruction, therefore, it was decided not to let participants answer it independently preoperatively. However, at the 1-, 2-, 3- and 4-year follow-up moments this information was gathered. For all QoL outcomes, a higher score reflects a better QoL.

Quality of hearing

The QoH questionnaires included the VAS on hearing, the Speech, Spatial and Qualities of Hearing Scale (SSQ) and the Nijmegen Cochlear Implant Questionnaire (NCIQ)[19,20]. The VAS on hearing contains a thermometer for hearing, which results in a score between 0 and 1[18]. The SSQ consists of three subdomains. The SSQ1 comprises questions on speech understanding in quiet, in background noise, in reverberant environments and on the telephone. The SSQ2 comprises questions on spatial hearing; identifying directions of sounds and distance approximation, and the SSQ3 comprises questions on the QoH. The results are three subdomain scores ranging from 0 to 10[19,21]. The NCIQ contains six subdomains of hearing: (1) Basic sound perception, (2) Advanced sound perception (in difficult daily listening situations or background noise), (3) Speech production, (4) Self-esteem, (5) Activity limitations, (6) Social interaction[20]. The results are subdomain scores ranging from 0 to 100[20,21]. As this questionnaire is specifically designed for the evaluation after cochlear implantation, this questionnaire was not administered at baseline. For all QoH outcomes, a higher score reflects a greater ability.

Tinnitus

The tinnitus questionnaires included the Tinnitus Handicap Inventory (THI) and Tinnitus Questionnaire (TQ)[22,24]. The THI is a questionnaire regarding tinnitus handicap in daily life. The questionnaire comprises a 12-item functional subscale, an 8-item emotional subscale and a 5-item catastrophic subscale[22,24,25]. The TQ consists of 52 questions on emotional and cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbance and somatic complaints[23]. Both tinnitus questionnaires were administered to all participants, but could only be completed when a participant experienced tinnitus.

Sample size calculation

Sample size was calculated before the start of the trial using a *T*-test analysis of the primary outcome measure. Fourteen participants in each group were needed to detect a clinically relevant difference of 3 dB in SRTn between groups on the speech perception-in-noise coming from a source in front of the participant test with a standard deviation of 3 dB, an alpha of 0.05 and a power of 80%. Five additional subjects were included per group to compensate for any potential unexpected loss to follow-up[8-10].

Missing data and loss to follow-up

In case participants were lost to follow-up, analyses were performed with (intention to treat) and without these missing data as a sensitivity analysis.

Statistical analysis

Prior to analysis, all data were double-checked by two researchers independently. Patient characteristics were presented as counts, percentages, and medians with interquartile ranges (IQRs).

All outcome measures were analyzed longitudinally (follow-up points 1, 2, 3 and 4 years) via a linear regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type, using a maximum likelihood estimation method). The tinnitus outcomes were analyzed longitudinally via a logistic regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type), as the outcome was dichotomized: the presence of tinnitus burden (yes or no). A participant was considered to experience tinnitus burden when a score higher than 0 was reached on either of the questionnaires.

All models included time (as a categorical variable), group (simBiCI versus UCI/seqBiCI), the interaction between time and group (to study whether the course of scores differed between the study groups) and baseline score of the particular outcome (to adjust for possible baseline differences). Since the TTO and NCIQ were not administered at baseline, the VAS on health and VAS on hearing scores were used as baseline scores. For the speech perception-in-noise and localization tests the CVC phoneme scores were used. HA use (yes/no) at baseline (before the study) was the only variable which differed significantly between groups[8-10] and for that reason, this variable was added to all models to verify whether it was a possible confounder. Sex and age may have been related to some of the outcomes discussed in this manuscript. If so, sex and age would have also been related to the baseline outcomes. Since we corrected for baseline outcomes, no additional corrections for sex and age were performed. Residuals of the final linear models were checked for normality and showed a normal distribution. To visualize the course of all behavioral and self-reported outcomes for both study groups, all outcome measures were graphed, presenting mean outcome values with standard deviations.

A *p*-value <0.05 was considered statistically significant. The regression models were generated in SPSS version 22.0 whereas the residue analyses were performed in SAS version 9.4.

RESULTS

Participant characteristics

Between December 2009 and September 2012, 512 patients were assessed for eligibility. Forty participants were randomized and 19 participants were included in each group (Figure 1). Characteristics of participants are described in Table 1[8-10]. As previously mentioned, the groups were similar at baseline except for the number of participants using a HA (19 vs 15).

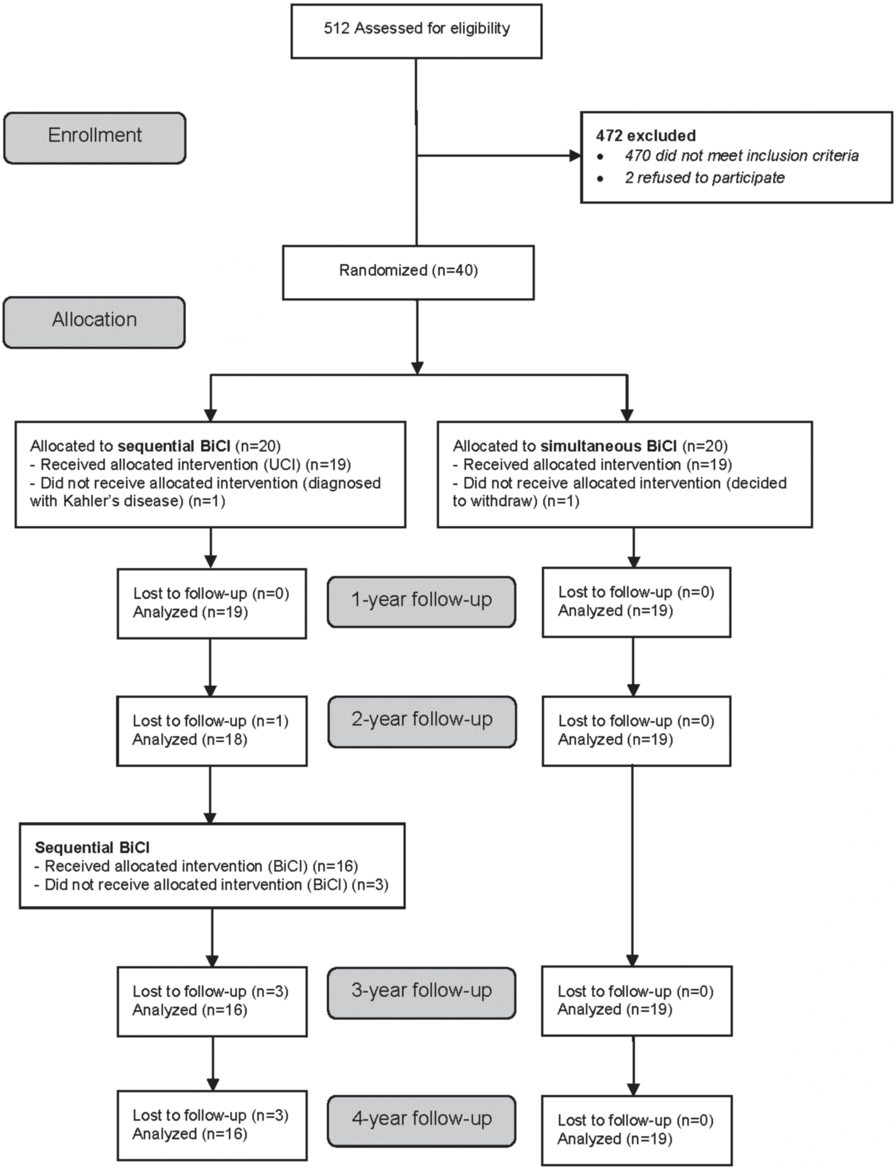

Figure 1 | Flowchart of enrollment

simBiCI = simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral/ sequential bilateral cochlear implantation

Table 1| Characteristics of participants at time of inclusion in the study

	UCI/SeqBiCI Median [IQR]	**SimBiCI Median [IQR]**
Male:Female	11:08	08:11
Age at inclusion (yrs)	54 [43-64]	52 [36-63]
Duration of severe HL AD (yrs)	17 [9-33]	16 [11-25]
Duration of severe HL AS (yrs)	18 [9-35]	16 [11-25]
First CI, right:left	6:13	17:2
PTA AD (dB)	106 [94-111]	106 [89-119]
PTA AS (dB)	108 [93-114]	108 89-120]
CVC phoneme score with hearing aids (%)	44 [29-56]	48 [24-63]
HA use year 0, yes:no	19:0	15:4
HA use year 1, yes:no	12:7	Not applicable
HA use year 2, yes:no	13:5 (1 LTFU)	Not applicable
Treatment Hospital		
Utrecht	11	8
Maastricht	4	5
Nijmegen	2	3
Leiden	1	2
Groningen	1	1
Cause of deafness		
Hereditary	7	9
Unknown and progressive	9	6
Sudden Deafness	0	2
Head trauma	0	1
Meningitis	2	0
Rhesus Antagonism	1	0
Sound exposure	0	1

BiCI: bilateral cochlear implantation; yrs: years; AD: auricus dexter; AS: auriculus sinistra; PTA: pure tone average over 1, 2 and 4 kilohertz; CVC: consonant vowel consonant; CI: cochlear implant; LTFU: lost to follow-up; Hz: hertz; IQR: interquartile ranges.

Missing data and loss to follow-up

During the second and third year of follow-up, two participants in the UCI/seqBiCI group withdrew for personal reasons. A third participant was excluded from the UCI/seqBiCI group because of poor performance with the first implant. This participant appeared to have a hearing loss due to rhesus antagonism and was expected not to benefit from a second CI because of this central cause of deafness (Figure 1)[8-10].

At year 1 the 15° localization results were missing in one participant in the simBiCI group. A cut-off of 30dB for speech perception scores was used for one participant in each group. At year 3 the results of the VAS health and hearing were missing in one participant in the simBiCI group and the TTO was missing for another participant in this group. At year 4 the EQ-5D was missing for one participant in the simBiCI group and TTO was missing for another participant in this group.

Behavioral outcomes

Figure 2 shows all behavioral outcomes during the 4 years follow-up for both study groups. Group differences, course per group and difference between follow-up moments per group were analyzed using the previously mentioned linear regression analysis with an autoregressive residual covariance matrix (Table 2). In the UCI/seqBiCI group, 10 and 11 out of 16 participants used a contralateral hearing aid at year 1 and year 2 respectively.

Scores are presented in mean values with an error bar representing the standard deviation. SISSS: Speech intelligibility-in-noise from spatially separated sources; WPS: worst performance situation; BPS: best performance situation; CVC: consonant vowel consonant; yr: year; CI: cochlear implant; SimBiCI = simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral cochlear implantation/sequential bilateral cochlear implantation group. To improve readability, the results of both groups are presented interleaved, yet follow-up moments were similar in both groups.

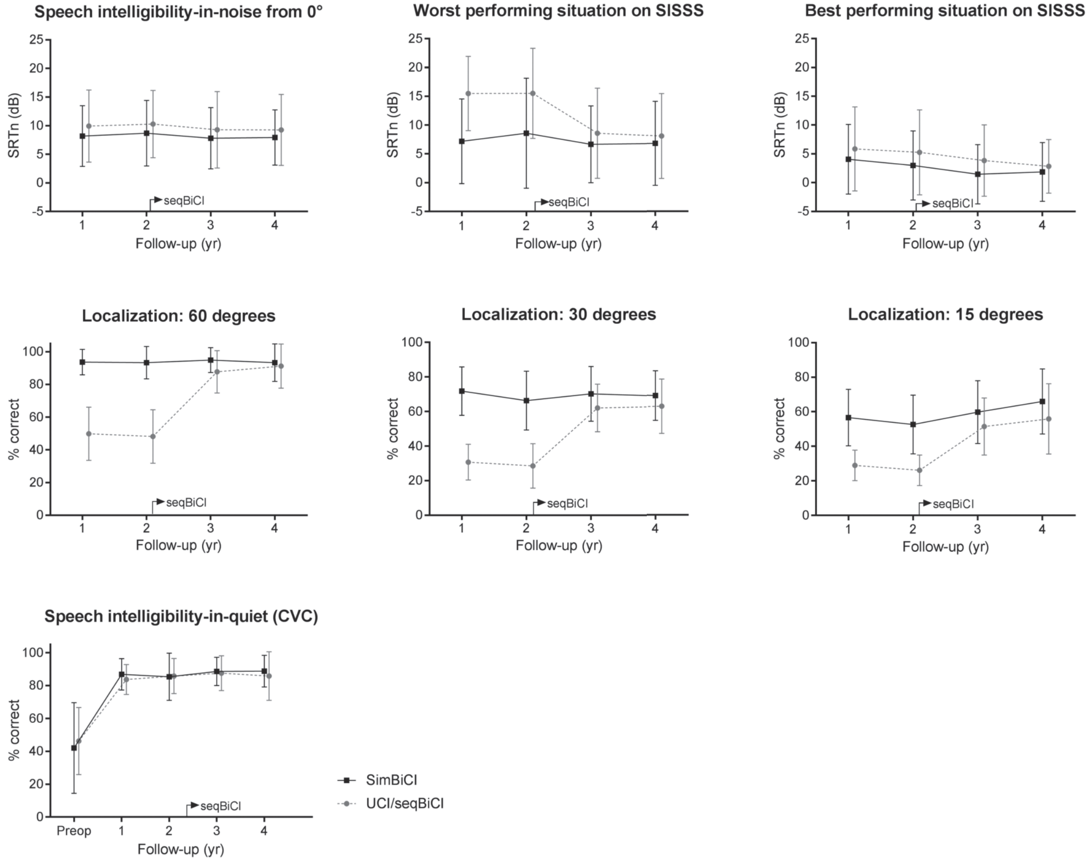

Figure 2 | Behavioral outcomes on hearing: a 4-year follow-up.

Scores are presented in mean values with an error bar representing the standard deviation. EQ5D: Dutch EuroQol-5D; HUI3: Health Utilities Index 3; VAS: Visual analogue scale; TTO: Time trade off; yr: year; CI: cochlear implant; SimBiCI = simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral cochlear implantation/sequential bilateral cochlear implantation group. To improve readability, the results of both groups are presented interleaved, yet follow-up moments were similar in both groups.

Table 2 | Results from a linear regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type) for all behavioral outcomes.

	Parameter	Mean	SD	Lower bound 95% CI	Upper bound 95% CI	P-value
Speech perception in noise from directly in front (dB)	Treatment	1.99	1.77	-1.55	5.53	.265
	Year 2	0.49	1.22	-1.91	2.91	.686
	Year 3	-0.38	1.05	-2.45	1.69	.718
	Year 4	-0.81	0.80	-2.41	0.78	.314
	Seq x year 2	-0.18	1.74	-3.63	3.26	.916
	Seq x year 3	-0.23	1.51	-3.23	2.76	.877
	Seq x year 4	0.02	1.16	-2.27	2.32	.986
	CVC baseline	-0.06	0.03	-0.12	0.01	.076
SISSS: WPS (dB)	Treatment	8.70	2.37	3.96	13.44	**<.001**
	Year 2	1.51	1.76	-1.97	4.99	.391
	Year 3	-0.41	1.53	-3.43	2.61	.787
	Year 4	-0.58	1.19	-2.94	1.77	.623
	Seq x year 2	-1.50	2.51	-6.47	3.47	.551
	Seq x year 3	-6.83	2.21	-11.20	-2.45	.002
	Seq x year 4	-7.06	1.71	-10.44	-3.67	**<.0001**
	CVC baseline	-0.07	0.04	-0.15	0.02	.113
SISSS: BPS (dB)	Treatment	0.79	1.96	-3.14	4.72	.688
	Year 2	-1.07	1.40	-3.84	1.70	.447
	Year 3	-2.60	1.22	-5.01	0.19	.035
	Year 4	-2.68	0.95	-4.56	-0.80	**.006**
	Seq x year 2	0.34	2.00	-3.62	4.29	.866
	Seq x year 3	0.48	1.76	-3.01	3.97	.786
	Seq x year 4	-0.60	1.37	-3.31	2.11	.663
	CVC baseline	-.012	0.04	-0.20	-0.03	**.009**
	HA use	7.05	3.42	0.10	14.00	**.047**
Localization, 15° (% correct)	Treatment	-27.87	5.01	-37.80	-17.94	**<.0001**
	Year 2	-3.98	4.81	-13.50	5.54	.410
	Year 3	3.21	4.54	-5.77	12.19	.481
	Year 4	9.09	3.96	1.23	16.94	**.024**
	Seq x year 2	1.12	6.82	-12.39	14.60	.870
	Seq x year 3	19.64	6.53	6.72	32.56	**.003**
	Seq x year 4	17.85	5.63	6.69	29.01	**.002**
	CVC baseline	0.05	0.07	-0.09	0.19	.493

	Parameter	**Mean**	**SD**	**Lower bound 95% CI**	**Upper bound 95% CI**	**P-value**
Localization, 30° (% correct)	Treatment	-41.09	4.56	-50.12	-32.06	**<.0001**
	Year 2	-5.45	4.36	-14.06	3.16	.213
	Year 3	-1.53	4.09	-9.63	6.56	.709
	Year 4	-2.25	3.53	-9.27	4.77	.526
	Seq x year 2	3.24	6.21	-9.02	15.51	.602
	Seq x year 3	34.20	5.93	22.48	45.92	<.0001
	Seq x year 4	35.73	5.07	25.67	45.79	**<.0001**
	CVC baseline	0.01	0.07	-0.12	0.14	.905
Localization, 60° (% correct)	Treatment	-44.45	3.88	-52.15	-36.74	**<.0001**
	Year 2	-0.35	3.66	-7.58	6.87	.923
	Year 3	1.23	3.40	-5.50	7.96	.719
	Year 4	-0.13	2.89	-5.89	5.62	.963
	Seq x year 2	-1.37	5.21	-11.67	8.93	.793
	Seq x year 3	38.26	4.93	28.52 –	48.01	**<.0001**
	Seq x year 4	43.04	4.15	34.78 –	51.29	**<.0001**
	CVC baseline	0.14	0.06	0.02 –	0.26	**.020**
CVC score (%)	Treatment	-3.72	3.34	-10.33 –	2.88	.267
	Year 2	-1.47	3.34	-8.07 –	5.12	.659
	Year 3	1.79	3.34	-4.81 –	8.39	.536
	Year 4	2.24	3.44	-4.54 –	9.04	.514
	Seq x year 2	3.56	4.75	-5.84 –	12.95	.455
	Seq x year 3	2.14	4.83	-7.40 –	11.69	.658
	Seq x year 4	-0.13	4.90	-9.81 –	9.55	.979
	CVC baseline	0.14	0.04	0.06 –	0.21	**<.001**

Reference treatment group = simBiCI; reference year = year 1. The final model contained the following variables: time + treatment + time x treatment + baseline CVC phoneme score. In case there was a confounding role for hearing aid use at baseline, this variable was included in the final model as well. SISSS: speech intelligibility-in-noise from spatially separated sources; CVC: consonant vowel consonant; HA: hearing aid; SimBiCI = simultaneous bilateral cochlear implantation; seq = unilateral cochlear implantation/sequential bilateral cochlear implantation group. Bold value means statistical significance.

Speech perception in noise

Speech perception in noise coming from a source in front of the participant did not differ significantly between UCI/seqBiCI and simBiCI over time (1.99 dB [-1.55 – 5.53], *p*=.265). The course of the SRTn did not differ significantly between the two groups and for both groups the SRTns remained stable over time.

In the WPS of the SISSS test, the UCI/seqBiCI group performed significantly worse over time: 8.70 dB [3.96 – 13.44], *p*<.001. A significant improvement was seen in the UCI/seqBiCI group after receiving CI2 (year 3 (seqBiCI) vs year 1 (UCI); -6.83 dB [-11.20 – -2.45], *p*=.002). In the BPS of the SISSS test however, no difference between groups over time was found, yet a significant improvement was seen in the simBiCI group after years 3 and 4 compared to year 1 (year 4 vs year 1: -2.68 dB [-4.56 – -0.80], *p*=.006). HA use at baseline was a significant confounder for the SISSS BPS, and therefore the final model was corrected for HA use.

Localization

The largest differences between groups were seen on the localization tests over time, for example in the 60 degrees configuration: the scores of UCI/seqBiCI were significantly lower (-44.45% [-52.15 – -36.74], p<.0001) than the scores of the simBiCI group over time. The UCI/seqBiCI group showed a significant improvement after receiving CI2, which is most evident between year 4 and year 1: 43.04% [34.78 – 51.29], p<.0001. The direction and significance of the results of the localization tests in 15 and 30 degrees configurations did not differ from the 60 degrees results.

Speech perception in quiet

The CVC phoneme scores did not differ significantly between groups over time. Also, the course of these scores did not differ significantly between groups and for both groups the scores were stable over time.

Self-reported outcomes

Quality of life outcomes

Figure 3 shows the QoL outcomes preoperatively and during the 4 years of follow-up for both study groups. The EQ-5D, HUI3 and VAS general health scores did not differ significantly between the UCI/seqBiCI and simBiCI group over time (Table 3). Also the course of these scores did not differ between groups and for both groups the EQ-5D, HUI3 and VAS general scores remained stable over time.

The TTO score was significantly lower in the UCI/seqBiCi group compared with the simBiCI group over time (-0.078 [-0.140 - -0.017], *p*=.017). A significant improvement was seen in the UCI/seqBiCI group after receiving CI2 (year 3 vs year 1: 0.084 [0.003- 0.165], *p*=.017). HA use was a significant confounder for the HUI3, and therefore the final model was corrected for HA use.

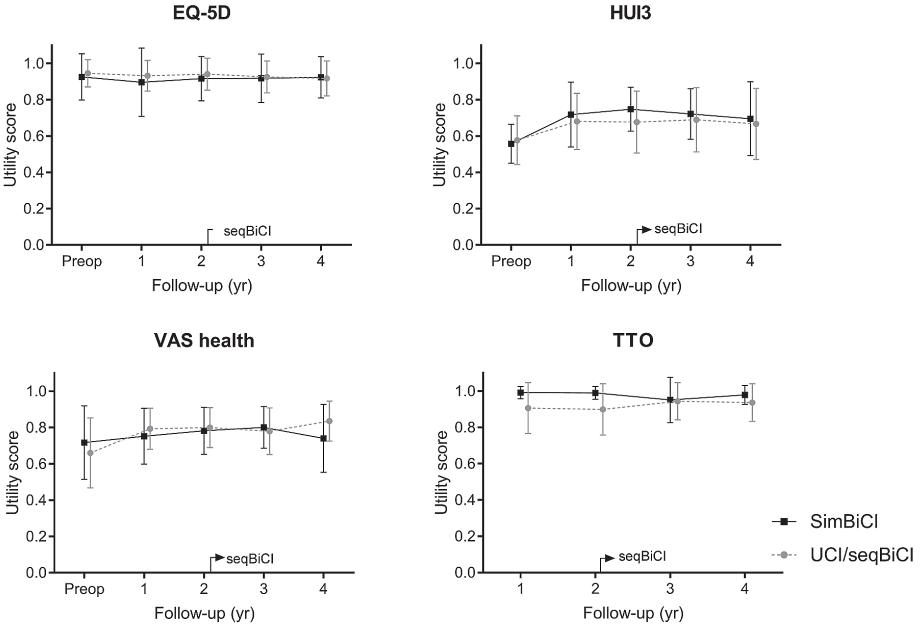

Figure 3 | Self-reported outcomes on quality of life: a 4-year follow-up.

Scores are presented in mean values with an error bar representing the standard deviation. EQ5D: Dutch EuroQol-5D; HUI3: Health Utilities Index 3; VAS: Visual analogue scale; TTO: Time trade off; yr: year; CI: cochlear implant; SimBiCI = simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral cochlear implantation/sequential bilateral cochlear implantation group. To improve readability, the results of both groups are presented interleaved, yet follow-up moments were similar in both groups.

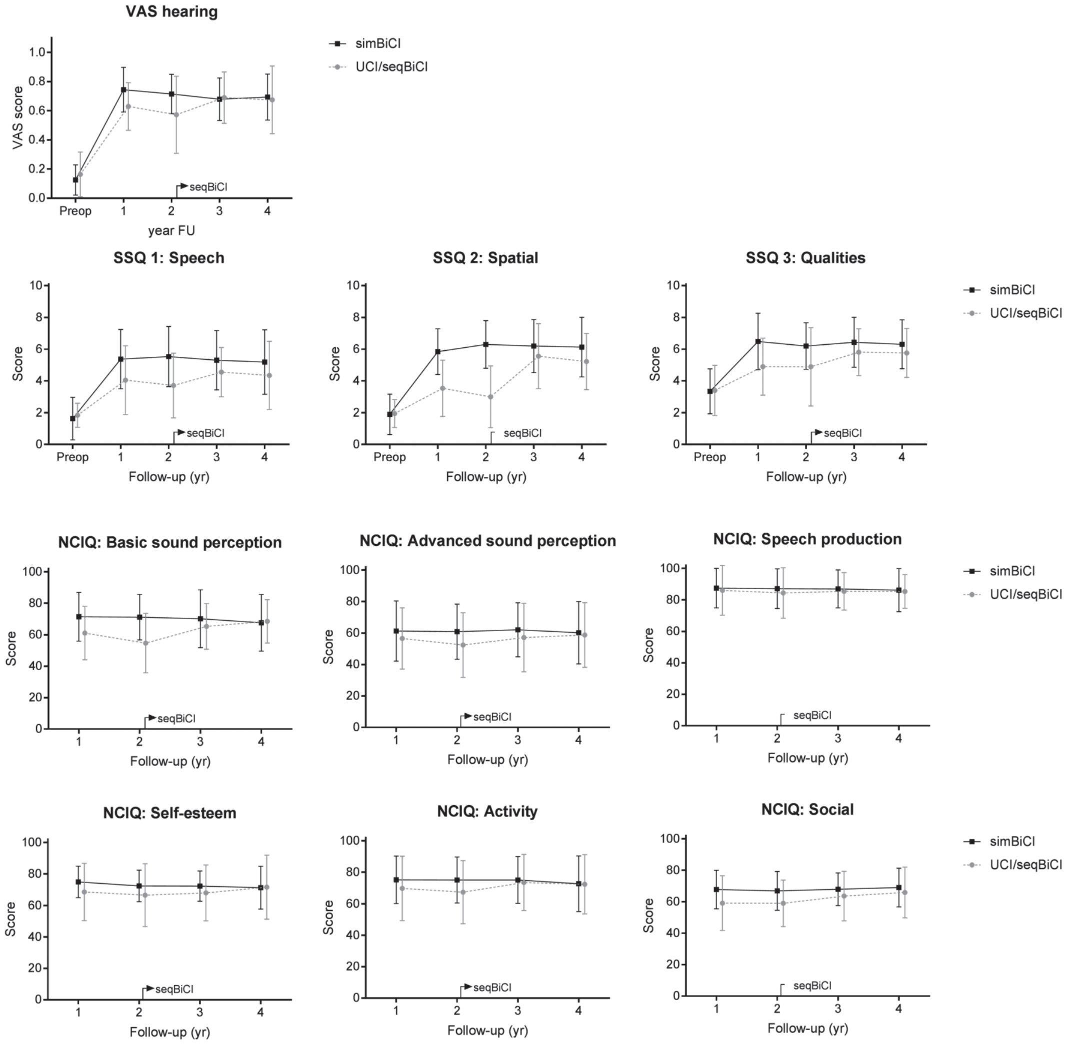

Figure 4 | Self-reported outcomes on quality of hearing: a 4-year follow-up.

Scores are presented in mean values with an error bar representing the standard deviation. VAS: visual analogue scale; SSQ: Speech, Spatial and Qualities Hearing Scale; NCIQ: Nijmegen Cochlear Implant Questionnaire; yr: year; CI: cochlear implant; SimBiCI = simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral cochlear implantation/sequential bilateral cochlear implantation group. To improve readability, the results of both groups are presented interleaved, yet follow-up moments were similar in both groups.

Quality of hearing outcomes

Figure 4 shows the QoH outcomes preoperatively and during the 4 years of follow-up for both study groups. The VAS hearing scores differed significantly between the UCI/seqBiCI and simBiCI group over time (-0.12 [-0.24 - -0.01], *p*=.036) (Table 4). The course of these scores did not differ between groups. The scores in the UCI/seqBiCI group did not improve significantly after receiving CI2.

The SSQ1, SSQ2 and SSQ3 scores were significantly lower in the UCI/seqBiCI group compared with the simBiCI group over time (most evident for SSQ2: -2.32 [-3.38 - -1.26], *p*=<.001). A significant improvement was seen in the UCI/seqBiCI group after receiving CI2 for the SSQ1 (year 4 vs year 1: 0.75 [0.10 – 1.41], *p*=.025) and the SSQ 2 and 3 (years 3 and 4 vs year 1, for example year 3 vs year 1 for SSQ2: 1.82 [0.60 – 3.04], *p*=.004). In the simBiCI group, all SSQ scores remained stable in the 4 years of follow-up.

The social interaction score of the NCIQ was significantly lower in the UCI/seqBiCI group compared with the simBiCI group over time (-9.26 [-18.20 - -0.33], *p*=.042). Significant increases in basic sound perception, self-esteem, activity and social interaction scores were seen in the seqBiCI group after receiving CI2 (year 4 vs year 1, most evident for basic sound perception: 12.22 [4.27 – 20.17], *p*=.003). In the simBiCI group, all NCIQ scores remained stable in the 4 years of follow-up.

Table 3 | Results from a linear regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type) for quality of life outcomes.

	Parameter	**Mean**	**Standard deviation**	**Lower bound 95% CI**	**Upper bound 95% CI**	***p*-value**
EQ-5D	Treatment	0.023	0.031	-0.038	0.083	.459
	Year 2	0.020	0.030	-0.038	0.079	.495
	Year 3	0.023	0.028	-0.033	0.079	.425
	Year 4	0.034	0.025	-0.016	0.083	.178
	Seq x Year 2	-0.009	0.042	-0.093	0.074	.825
	Seq x Year 3	-0.021	0.041	-0.102	0.061	.618
	Seq x Year 4	-0.038	0.036	-0.108	0.033	.296
	EQ-5D baseline	0.688	0.097	0.493	0.883	**<.0001**
HUI3	Treatment	-0.011	0.050	-0.112	0.089	.821
	Year 2	0.030	0.046	-0.060	0.120	.510
	Year 3	0.005	0.042	-0.079	0.088	.911
	Year 4	-0.022	0.035	-0.090	0.046	.525
	Seq x Year 2	-0.034	0.065	-0.162	0.095	.603
	Seq x Year 3	0.012	0.061	-0.109	0.133	.848
	Seq x Year 4	0.019	0.050	-0.081	0.119	.711
	HUI3 baseline	0.520	0.164	0.189	0.850	**.003**
	HA use	-0.172	0.068	-0.308	-0.036	**.014**
VAS health	Treatment	0.053	0.040	-0.026	0.132	.186
	Year 2	0.030	0.035	-0.039	0.099	.394
	Year 3	0.048	0.032	-0.015	0.112	.135
	Year 4	-0.012	0.025	-0.062	0.038	.647
	Seq x Year 2	-0.021	0.050	-0.120	0.078	.672
	Seq x Year 3	-0.062	0.046	-0.154	0.029	.179
	Seq x Year 4	0.053	0.037	-0.020	0.126	.155
	VAS health baseline	0.210	0.077	0.054	0.365	**.009**
TTO	Treatment	-0.078	0.031	-0.140	-0.017	**.013**
	Year 2	-0.002	0.030	-0.061	0.057	.958
	Year 3	-0.040	0.029	-0.096	0.017	.169
	Year 4	-0.012	0.024	-0.060	0.036	.627
	Seq x Year 2	-0.005	0.043	-0.089	0.079	.913
	Seq x Year 3	0.084	0.041	0.003	0.165	**.043**
	Seq x Year 4	0.047	0.035	-0.023	0.117	.183
	VAS health baseline	0.124	0.053	0.017	0.231	**.025**

Reference treatment group = simBiCI. Reference year = year 1. The final model contained the following variables: time + treatment + time x treatment + baseline score. In case there was a confounding role for hearing aid use at baseline, this variable was included in the final model as well. EQ-5D: EuroQol five-dimensional questionnaire; HUI3: the Health Utilities Index mark 3; HA: hearing aid; VAS: Visual Analogue Scale on general health; TTO: Time Trade-off; SimBiCI = simultaneous bilateral cochlear implantation; seq = unilateral cochlear implantation/sequential bilateral cochlear implantation group. Bold value means statistical significance.

Table 4 | Results from a linear regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type) for quality of hearing outcomes.

	Parameter	**Mean**	**Standard deviation**	**Lower bound 95% CI**	**Upper bound 95% CI**	***p*-value**
VAS hearing	Treatment	-0.122	0.057	-0.236	-0.008	**.036**
	Year 2	-0.029	0.052	-0.132	0.074	.581
	Year 3	-0.056	0.048	-0.152	0.040	.249
	Year 4	-0.050	0.039	-0.127	0.027	.198
	Seq x Year 2	-0.028	0.075	-0.175	0.120	.710
	Seq x Year 3	0.128	0.070	-0.010	0.266	.069
	Seq x Year 4	0.107	0.056	-0.005	0.220	.060
	VAS hearing baseline	0.201	0.166	-0.132	0.534	.232
SSQ1	Treatment	-1.524	0.533	-2.591	-0.458	**.006**
	Year 2	0.161	0.356	-0.542	0.865	.651
	Year 3	-0.063	0.304	-0.665	0.538	.835
	Year 4	-0.183	0.225	-0.630	0.263	.418
	Seq x Year 2	-0.409	0.508	-1.414	0.597	.423
	Seq x Year 3	0.831	0.440	-0.041	1.703	.062
	Seq x Year 4	0.750	0.330	0.096	1.405	**.025**
	SSQ1 baseline	0.984	0.220	0.540	1.429	**<.0001**
SSQ2	Treatment	-2.319	0.534	-3.380	-1.259	**<.0001**
	Year 2	0.460	0.472	-0.473	1.392	.332
	Year 3	0.357	0.426	-0.485	1.200	.403
	Year 4	0.291	0.336	-0.376	0.959	.389
	Seq x Year 2	-0.999	0.673	-2.328	0.331	.140
	Seq x Year 3	1.824	0.617	0.604	3.044	**.004**
	Seq x Year 4	1.543	0.492	0.567	2.520	**.002**
	SSQ2 baseline	0.421	0.190	0.039	0.803	**.032**
SSQ3	Treatment	-1.623	0.550	-2.723	-0.523	**.005**
	Year 2	-0.288	0.401	-1.081	0.505	.474
	Year 3	-0.087	0.346	-0.772	0.598	.802
	Year 4	-0.229	0.259	-0.743	0.284	.378
	Seq x Year 2	0.307	0.565	-0.811	1.425	.588
	Seq x Year 3	1.051	0.494	0.072	2.029	**.036**
	Seq x Year 4	1.205	0.374	0.463	1.947	**.002**
	SSQ3 baseline	0.473	0.161	0.146	0.800	**.006**

Table 4 | Continued.

	Parameter	Mean	Standard deviation	Lower bound 95% CI	Upper bound 95% CI	*p*-value
NCIQ basic	Treatment	-9.620	5.315	-20.218	0.978	.075
	Year 2	-0.263	4.119	-8.406	7.879	.949
	Year 3	-1.316	3.601	-8.441	5.810	.715
	Year 4	-3.863	2.737	-9.292	1.565	.161
	Seq x Year 2	-5.513	5.881	-17.139	6.112	.350
	Seq x Year 3	6.352	5.216	-3.970	16.673	.226
	Seq x Year 4	12.222	4.009	4.273	20.171	**.003**
	VAS hearing baseline	-19.889	17.165	-54.545	14.767	.253
NCIQ advanced	Treatment	-3.523	6.426	-16.391	9.345	.586
	Year 2	-0.376	4.049	-8.383	7.631	.926
	Year 3	0.764	3.456	-6.076	7.605	.825
	Year 4	-1.034	2.558	-6.106	4.038	.687
	Seq x Year 2	-3.124	5.787	-14.569	8.322	.590
	Seq x Year 3	2.485	5.006	-7.425	12.394	.621
	Seq x Year 4	5.969	3.747	-1.460	13.398	.114
	VAS hearing baseline	7.293	21.821	-36.823	51.410	.740
	HA use	-7.025	9.622	-26.485	12.436	.470
NCIQ speech	Treatment	0.680	4.581	-8.497	9.857	.883
	Year 2	-0.340	2.785	-5.848	5.168	.903
	Year 3	-0.559	2.368	-5.248	4.129	.814
	Year 4	-1.334	1.746	-4.796	2.128	.447
	Seq x Year 2	-1.014	3.981	-8.888	6.861	.799
	Seq x Year 3	-2.524	3.430	-9.316	4.267	.463
	Seq x Year 4	-1.785	2.558	-6.856	3.286	.487
	VAS hearing baseline	-29.738	15.691	-61.456	1.980	.065
	HA use	-4.760	6.921	-18.754	9.234	.496
NCIQ self esteem	Treatment	-6.806	4.844	-16.488	2.877	.165
	Year 2	-2.602	3.346	-9.218	4.013	.438
	Year 3	-2.635	2.873	-8.321	3.051	.361
	Year 4	-3.684	2.140	-7.928	0.559	.088
	Seq x Year 2	0.713	4.781	-8.741	10.167	.882
	Seq x Year 3	2.618	4.161	-5.618	10.855	.530
	Seq x Year 4	7.084	3.135	0.869	13.299	**.026**
	VAS hearing baseline	10.330	16.380	-22.770	43.429	.532

Table 4 | Continued.

	Parameter	Mean	Standard deviation	Lower bound 95% CI	Upper bound 95% CI	*p*-value
NCIQ activity	Treatment	-6.147	5.595	-17.338	5.044	.276
	Year 2	-0.150	3.796	-7.656	7.357	.969
	Year 3	-0.124	3.252	-6.562	6.313	.970
	Year 4	-2.476	2.417	-7.269	2.317	.308
	Seq x Year 2	-1.719	5.425	-12.447	9.009	.752
	Seq x Year 3	6.108	4.411	-3.217	15.433	.197
	Seq x Year 4	7.802	3.540	0.783	14.822	**.030**
	VAS hearing baseline	18.473	19.026	-20.007	56.953	.338
NCIQ social	Treatment	-9.264	4.471	-18.201	-0.327	**.042**
	Year 2	-0.804	3.149	-7.031	5.423	.799
	Year 3	0.157	2.711	-5.209	5.523	.954
	Year 4	1.308	2.025	-2.708	5.325	.520
	Seq x Year 2	0.954	4.499	-7.943	9.850	.832
	Seq x Year 3	5.790	3.927	-1.982	13.563	.143
	Seq x Year 4	7.074	2.966	1.191	12.956	**.019**
	VAS hearing baseline	15.457	15.016	-14.913	45.827	.310

Reference treatment group = simBiCI. Reference year = year 1. The final model contained the following variables: time + treatment + time x treatment + baseline score. In case there was a confounding role for hearing aid use at baseline, this variable was included in the final model as well. VAS: Visual Analogue Scale on hearing; SSQ: Speech, Spatial and Qualities of Hearing Scale; NCIQ: Nijmegen Cochlear Implant Questionnaire; HA: hearing aid; SimBiCI = simultaneous bilateral cochlear implantation; seq = unilateral cochlear implantation/sequential bilateral cochlear implantation group. Bold value means statistical significance.

Tinnitus outcomes

Figure 5 shows the prevalence of tinnitus burden preoperatively and during the 4 years of follow-up for both study groups. Although the prevalence appears larger in de simBiCI group, the prevalence of tinnitus burden, corrected for baseline prevalence, did not differ significantly between the UCI/seqBiCI and simBiCI group over time. Also the course of tinnitus burden did not differ between groups and for both groups the presence of tinnitus burden remained stable in the 4 years of follow-up (Table 5).

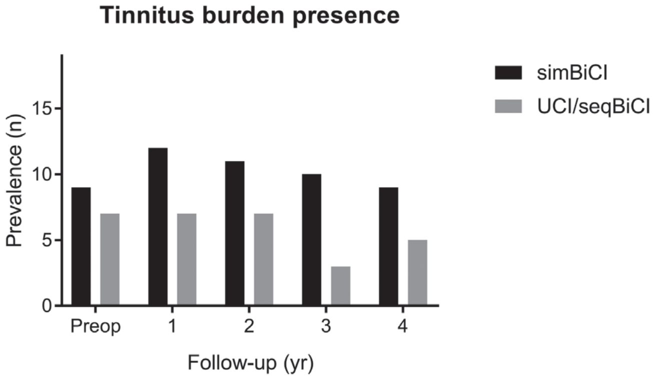

Figure 5 | Tinnitus outcomes: a 4-year follow-up.

The number of participants with the presence of tinnitus burden. The presence of tinnitus burden is defined as a score higher than 0 on either one of the questionnaires. SimBiCI = simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral cochlear implantation/sequential bilateral cochlear implantation group.

Table 5 | Results from a logistic regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type) for the presence of tinnitus burden.

Parameter	Mean	Standard deviation	Odds ratio	Lower bound 95% CI	Upper bound 95% CI	*p*-value
Treatment	-1.110	0.7918	0.330	0.070	1.556	.161
Year 2	-0.278	0.5155	0.758	0.276	2.080	.590
Year 3	-0.578	0.6006	0.561	0.173	1.822	.336
Year 4	-0.869	0.6452	0.419	0.118	1.485	.178
Seq x Year 2	0.637	0.6122	1.891	0.569	6.277	.298
Seq x Year 3	-0.833	0.8966	0.435	0.075	2.520	.353
Seq x Year 4	0.610	0.7606	1.840	0.414	8.172	.423
Tinnitus baseline	2.404	0.7202	11.068	2.698	45.401	**.001**

Reference treatment group = simBiCI. Reference year = year 1. The final model contained the following variables: time + treatment + time x treatment + baseline tinnitus burden presence. SimBiCI = simultaneous bilateral cochlear implantation; seq = unilateral cochlear implantation/sequential bilateral cochlear implantation group. Bold value means statistical significance.

Sensitivity analysis

A sensitivity analysis of the behavioral and self-reported data without participants with missing data revealed no differences regarding direction, effect sizes or significance of the results compared to the primary analysis except for the NCIQ basic sound perception: a significant overall lower NCIQ basic sound perception score was seen in the UCI/seqBiCI group (-11.61, *p*= .028). This indicates that missing data in the original analyses did not obscure the results.

Complications

As shown in Table 6, several complications occurred during the 4 years follow-up period. One participant suffered from vertigo 1 year following simBiCI. Electronystagmographic examination was inconclusive, yet vestibular areflexia was excluded as the cause of vertigo. In one participant in the UCI/seqBiCI group, the left CI had to be explanted and re-implanted 4 years after initial implantation. After initial good performance, the left CI became dysfunctional resulting in an increased stimulation level and coexisting facial nerve stimulation. The cause of this failure remained unclear, imaging and integrity tests were normal. One participant in the simBiCI group with a history of panhypopituitarism, hypothyroidism, kidney failure and systemic lupus erythematosus for which corticosteroids were used, suffered from skin flap necrosis after implantation of the left CI. Surgery was needed to close the subsequent skin defect. One participant suffered from a facial nerve palsy 10 days after seqBiCI (House Brackmann grade 3), of unknown origin, possibly due to a viral infection. The palsy improved spontaneously to House Brackmann grade 2. Another participant in the UCI/seqBiCI group suffered from acute otitis media in the secondly implanted ear for which intravenous antibiotic treatment was needed. One participant in the UCI/seqBiCI group perceived extra sound sensations in CI2. In one participant in the UCI/seqBiCI group, local antibiotics had to be administered to treat a skin infection at the implantation site. In both groups, a participant experienced pain at the ear's helix due to pressure of the speech processor, for which a support frame and a body worn speech processor were provided. Although it appears that the complication rate is higher in de UCI/seqBiCI group, this was not statistically supported.

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Table 6. Complications that occurred in this randomized controlled trial during 4 years of follow-up.

Adverse events	SimBiCI	UCI/SeqBiCI	Onset of complication
Vertigo/dizziness	1	0	1 year after simBiCI
Dysfunction of cochlear implant	1	0	4 years after simBiCI
Flap necrosis leading to skin defect	0	1	10 months after seqBiCI
Facial nerve paresis	0	1	10 days after seqBiCI
Acute otitis media	0	1	Two weeks after seqBiCI
Pain	1	1	2 years after simBiCI; 5 months after UCI
Wound infection	0	1	Within 1 month after seqBiCI
Perception of extra sounds	0	1	Within 1 month after seqBiCI

SimBiCI = simultaneous bilateral cochlear implantation; UCI/seqBiCI = unilateral cochlear implantation/sequential bilateral cochlear implantation

DISCUSSION

Key findings

The current RCT evaluated the longitudinal behavioral and self-reported outcomes after simBiCI compared with UCI/seqBiCI, with a 2-year inter-implant interval, in adult patients with severe-to-profound bilateral SNHL with marginal benefit of conventional hearing aids (an aided CVC phoneme score of ≤50% at 65 dB SPL)

Three participants allocated to the UCI/seqBiCI group, did not proceed to seqBiCI. This study showed that speech perception in noise, localization abilities (SISSS WPS, localization) and self-reported results (SSQ 1 and 2 and NCIQ, social interaction domain) were significantly worse in the UCI/seqBiCI group compared to the simBiCI group over the course of the 4 year follow-up. This is associated with the poorer results obtained by the UCI/seqBiCI group in the first two years of unilateral CI use. In the UCI/seqBiCI group, a significant improvement of these scores was seen after receiving CI2. With this improvement, the UCI/seqBiCI participants (with 2 years of bilateral experience) reached the same level as the simBiCI participants at 3 and 4 years of follow-up.

In one of 4 QoL questionnaires (TTO), a significantly lower utility score was found in the UCI/seqBiCI group compared to the simBiCI group over time. After the participants received CI2 in the seqBICI group, their TTO results reached to the level of the simBiCI group. The prevalence of tinnitus burden did not differ significantly between both groups over time.

Comparison with literature & clinical implication

In previous publications from our group, studying the differences between the BPS with one CI (with or without a contralateral hearing aid) and simBiCI[48,9], advantages of simBiCI over UCI on spatial speech perception and localization of sounds were demonstrated behaviorally and subjectively. Corresponding to existing observational studies and our previous article from this RCT, the present study identified that patients after seqBiCI also benefit from receiving a second CI as demonstrated in the spatial speech perception and localization of sounds tasks[26-29]. Thus, this study shows that after providing deaf patients with one CI, they still benefit from bilateral hearing after sequentially implanting a second CI within an inter-implant interval of 2 years.

No significant differences were found between simBiCI and seqBiCI at 4 years follow-up on behavioral and self-reported outcome measures tested. This finding does not advocate for one of these implantation modalities over the other. Therefore, when considering bilateral cochlear implantation, individual factors that might influence the choice for seqBiCI or simBiCI such as for example duration of anesthesia, the intensive rehabilitation, as well as the cost-effectiveness related with each intervention should be taken into account. Yet, delaying implantation of the second ear in our UCI/seqBiCI group did limit hearing in noise and localization capabilities in the two years of unilateral CI use. This might have real-life consequences in this timeframe. To our knowledge, the present study is the first to compare outcomes of simBiCI versus seqBiCI in an RCT.

The present findings encourage UCI patients with no or marginal benefit from hearing aids to receive a second CI in order to reach improved benefits in speech perception in noise and localization abilities. Thus, there is evidence that implant centers all over the world should consider seqBiCI for all their unilaterally implanted patients with marginal effect or no effect of a contralateral hearing aid. Even though longer duration of inter-implant interval is suggested to cause lesser benefit of CI2 compared to CI1, multiple studies have shown that bilateral results are better than unilateral results[26,28]. In the present study, the inter-implant interval did not differ between participants in this trial, therefore, the effect of duration of inter-implant interval was not investigated.

It has already been shown that spatial speech perception abilities continue to improve over time for at least 4 years after simBiCI[13,30]. Longitudinal results of our study are in line with these findings and show an increased performance in the optimal situation of the SISSS in the simBiCI group over time.

In this study, three participants did not proceed to seqBiCI after UCI. Previous data suggested that not all UCI patients proceed to seqBiCI[31]. Therefore, our study finding may be a realistic representation of the actual clinical population at various implant centers. Patients' withdrawal might be influenced by good performance with CI1, yet conversely, bad performance with CI1 could make patients reluctant to proceed to seqBiCI. Of the three participants in the UCI/seqBiCI group who did not proceed to seqBiCI, two were happy with the results after UCI and one participant who was deafened due to resus antagonism had such poor results with UCI that improvement after seqBiCI was not expected.

The lack of overall QoL improvement after seqBiCI in three out of four QoL questionnaires corresponds to earlier findings in literature[27]. QoL questionnaires are commonly used in RCTs to perform a cost-utility analysis. As confirmed by the current study, most general health utility instruments are not appropriate to measure changes after cochlear implantation[18,28,32]. For example, the EQ-5D and VAS health instruments do not incorporate a hearing element, and are therefore not sensitive to detect change in QoL as a result of cochlear implantation[10]. Moreover, ceiling effects of EQ-5D and TTO were observed, making it even more challenging to detect improvement. Thus, for RCTs on cost-utility analysis, the use of a QoL instrument with a hearing element in cochlear implant studies, for example the HUI3, seems appropriate[10,30]. As illustrated in Figure 3, HUI3 scores improved after UCI and simBiCI when compared to the situation before implantation. This finding corresponds to previously published data[10]. Nonetheless, to detect smaller differences, such as the additional effect of a second CI in the UCI/seqBiCI group or differences between simBiCI and seqBiCI the HUI3 is not sensitive enough. Compared to QoL questionnaires, QoH questionnaires detected the largest benefit of cochlear implantation, corresponding with previous findings[27,29].

The nature of the complications that occurred during our trial were in line with a previous study, in which vertigo, tinnitus and device failure were among the most reported complications after cochlear implantation[33]. Due to the low sample size, the complication rate could not accurately be compared with literature.

Strengths and limitations

The major strength of the current study is the study design. Since allocation bias is excluded, an RCT provides a high level of evidence (level I). Data were prospectively gathered at the same time points for all participants to ensure consistency in reported outcomes. Furthermore, the study design enabled us to examine multiple outcomes: BiCI versus UCI (and bimodal), simBiCI versus seqBiCI and UCI versus seqBiCI. Another strength is the longitudinal method for data analyses (GEE) since it generates more power to detect differences. These strengths add scientific value to knowledge based on previously published studies.

A possible limitation of this study is the relatively small sample size that made it difficult to detect differences in secondary outcomes. The sample size calculation was based on a power analysis aiming at the primary outcome measure. It was performed under the assumption that the increase in power due to repeated measurements would be sufficient for a time by intervention group interaction in the analysis, effectively describing and testing the intervention effect over time. We decided to calculate the sample size in this manner, since a sample size calculation for repeated measurement requires both accurate means (and standard deviations) of the outcome for each time point as well as the correlation (or covariance) between the measurements at different time points. An accurate estimate for especially the correlations was not available at the moment of conception of the trial in 2008. Longitudinal analyses however, have more power compared to cross-sectional analyses because of the repeated observations at the individual level. This approach may have compensated for the lack of power. Three participants were lost to follow-up. This could have led to a bias in treatment effect. However, the sample size calculation incorporated loss to follow-up up to five participants per group. Moreover, sensitivity analyses showed comparable results to the original analyses regarding effect sizes. The localization abilities were scored as percent correct in three different loudspeaker configurations. In retrospect, presenting these results as a mean error in degrees azimuth would be more valuable than a percent correct score. However, our set-up did not allow us to extract mean error data. Hearing aids were not fitted before every test session. In addition, the noise reduction method may have differed per participant. The rehabilitation was done according to the standards of each CI center. Since we used a block randomization per center, possible differences between centers could not have affected the outcome difference between groups. Another possible limitation is the use of logistic regression instead of linear regression for the tinnitus outcomes. Continuous data provide more information than dichotomous data. We only used the presence of tinnitus and not the THI and TQ scores. Since participants not suffering from tinnitus did not complete the questionnaires, the THI and TQ scores of these patients were lacking. Linear regression analysis with all these missing data would result in biased results.

CONCLUSION

In this RCT, we evaluated the behavioral and self-reported outcomes after simBiCI compared with UCI/seqBiCI in adult patients with severe-to-profound SNHL with marginal benefit of hearing aids (aided CVC phoneme score of ≤50%) longitudinally. In the first two years of this study, patients after UCI performed significantly worse than patients after simBiCI, on various spatial hearing and localization outcomes. They showed significant improvement after seqBiCI 2 years later and reached the same amount of benefit as the simBiCI group after 4 years of follow-up. Although the interval between sequential implantation was only 2 years, our results show a significant benefit of bilateral implantation both after simultaneous and sequential implantation over unilateral cochlear implantation with or without a contralateral HA.

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Conflict of interest statement and funding

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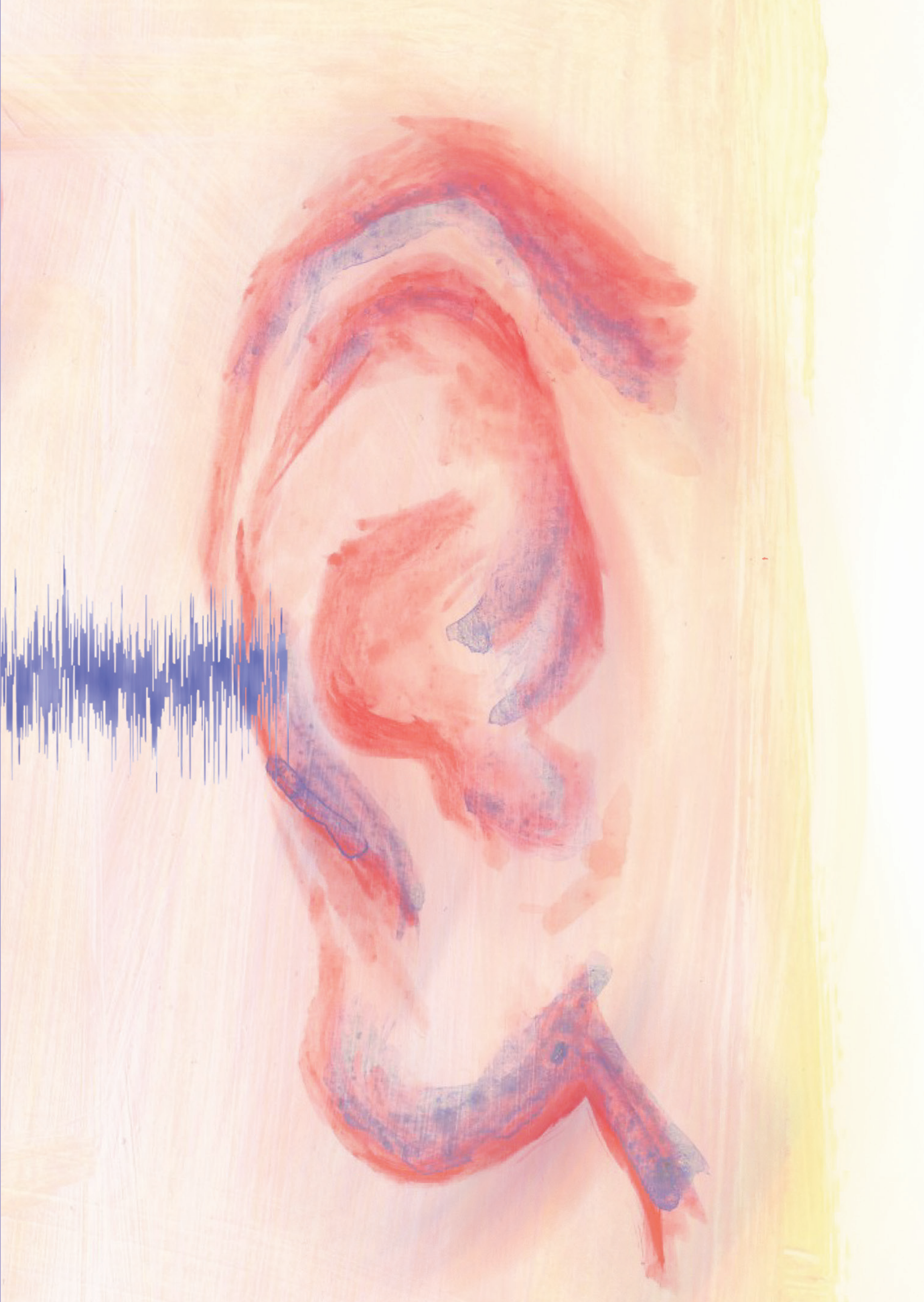
Chapter 8

General discussion



GENERAL DISCUSSION

Introduction

The general aim of this thesis was to improve the knowledge on the prognosis of adults with severe to profound hearing loss after both unilateral cochlear implantation (UCI) and bilateral cochlear implantation (BiCI). More specifically, we aimed to accomplish three things. First, we aimed to predict cochlear implantation outcomes based on pre-implant factors in order to improve patient counseling preoperatively as well as optimize inclusion criteria by retrospective analysis of data of many years of cochlear implantation experience in the UMC Utrecht. Second, we aimed to refine the knowledge on the functional benefit of BiCI over UCI in adult patients with severe to profound sensorineural hearing loss (SNHL). Third, we aimed to compare hearing results after simultaneous BiCI (simBiCI) versus sequential BiCI (seqBiCI) in the same patient population. This was done using data of a randomized controlled trial (RCT) designed to answer these questions.

UCI

Performance with a cochlear implant varies largely between implantees and is difficult to predict before implantation. The ability to predict CI performance before implantation would enable clinicians to improve preoperative counselling in future CI users. In **Chapter 2,** a cohort of unilateral implantees was evaluated retrospectively in order to determine which pre-implant characteristics are associated with post-implant speech perception performance.[1] This cohort was among the largest cohorts evaluating prognostics factors in unilateral CI studies. Contrary to the earlier studies[2,3], age at implantation was found not to influence post-implant outcomes. However, as expected, the duration of deafness did correlate with post-implant outcomes owing to the degeneration of spiral ganglion cells after longer periods of auditory deprivation, which is discussed in more detail later.[4–9] Ideally, a clinician would want to know the amount of spiral ganglion cells left intact after a period of auditory deprivation. Unfortunately, no such measurement is available in living human beings. Patients deafened by meningitis in the Netherlands are entitled to receive bilateral CIs soon after deafening since insertion of a CI electrode may be more challenging due to ossification of the cochlea.[10,11] In the study described in **Chapter 2** we showed that partial insertions of the electrode as well as the disease itself resulted in worse results in meningitis patients compared to recipients with other causes of hearing loss. Otosclerosis as cause of deafness was also found to be negatively associated with post-implant speech perception performance. Since merely an association was studied owing to the study design, the cause of this negative association was not investigated. These results advocate for more research on cochlear implantation in otosclerosis in order to investigate the variables underlying this outcome. As for side of implantation, **Chapter 3** showed proof of a right-ear advantage in the majority of the studied pediatric and adult population. Limitations of this systematic review are that studies were of low quality and no RCTs were included.[12] Nonetheless, none of these studies showed proof a left-side advantage. Since the majority of people are right-handed, it seems sensible to advise right ear implantation in situations where duration of deafness is similar between ears and no other factors favor one ear over the other.

SimBiCI versus UCI

There is an ongoing global discussion on whether or not BiCI should be standard clinical care for adult patients with bilateral severe to profound SNHL and whether these patients should receive their bilateral CIs simultaneously or sequentially. In this thesis we evaluated the difference in behavioral and self-reported outcomes between BiCI and UCI as well as simBiCI and seqBiCI. As seen in previous observational studies, clear advantages of BiCI over UCI were seen for localization of sound and speech perception in noise skills in the first 2 years of this RCT.[13,14] The largest behavioral benefit was seen in the ability to localize sounds. In our questionnaire results, localization skills improved the most in the UCI/seqBiCi group. Also the difference between the UCI and simBiCI group were most evident for questionnaires concerning localization of sounds. The Speech, Spatial and Qualities of Hearing Scale (SSQ) spatial subscale comprises questions on spatial hearing such as identifying directions of sounds and estimating distance. Not only the improvement of localization ability after the second cochlear implant was remarkable, but also the very low localization ability in the UCI group in the described testing conditions. For instance, the mean localization percent correct score for the UCI group in the 15 degrees configuration 2 years after UCI was 29% which underlines the difficulties experienced by unilateral CI implantees in situations such as traffic. However, a limitation of the behavioral outcome measures was the manner in which the localization data were handled. The localization test entailed three configurations, a 15 degrees angle between 5 loudspeakers, a 30 degrees angle between 5 loudspeakers and 60 degrees angle between 3 three loudspeakers. A participant was asked from which loudspeaker he or she thought a sound (*Hello, what's this?)* originated from. The loudspeaker the participant guessed was noted. Data were handled in a manner that a percent correct score was extracted, whereas degree specific data would be more valuable such as a difference score in azimuth between stimulus and response. In addition, only horizontal localization of sound was tested, whereas vertical localization was not taken into account. Future studies examining localization of sound abilities in CI users ought to use a test set-up in which both vertical and horizontal localization is tested and a difference scores between stimulus and response in azimuth or elevation is extracted.

The second largest benefit of simBiCI over UCI is the ability to understand speech perception in noise, as shown in the results of the speech intelligibility in noise from spatially separated sources (SISSS) (in the worst performing situation) and the results of the

SSQ speech subscale. Typically, inability to understand speech in noise is called the cocktail party effect, insinuating speech in noise problems occur in situations with many competing sounds. Yet, in the consultation room patients with a single CI already complain about the inability to understand speech in surroundings with just one competing speaker. This inability may well have societal impact as one cannot follow daily conversations in family or occupational setting with one CI. The subjective difficulties that unilateral or bilateral CI users experience are difficult to measure accurately due to a lack of (topic specific) patient related outcome measures (PROMs) which do address these settings/issues. This necessitates the establishment of core outcomes for these patients and evaluation of the measurement properties of existing instruments to measure these outcomes in detail. Unfortunately a cost-utility analysis based on the difference between bilateral and unilateral CIs on a societal level incorporating elements such as participation at work, in traffic and income generation was not possible in this RCT due to a lack of information on all these topics. Though, one can imagine that bilateral CIs from a society point of view become (cost-) effective after fewer years than when only measuring disability on a disease level.

SimBiCI versus seqBiCI

Chapters 4 and **Chapter 7** encompass studies examining the difference in results between simBiCI and seqBiCI with an inter-implant interval of 2 years. In the 4 years of follow-up, an average advantage over time of simBiCI over seqBiCI was seen for localization of sound in one of three administered conditions in the horizontal plane. For other outcome measures no significant differences were reported in favor of simBiCI, neither in the behavioral tests, nor the self-reported outcome measures.[15,16]

This is in contrast with the results of seqBiCI in children where sequential implantation has proven to be disadvantageous compared to simBiCI.[17] This disadvantage of seqBiCI is due to the fact that auditory pathways are not yet fully developed in the pediatric brain. The example of unilateral deafness is discussed in **Chapter 3**. Similar to unilateral deafness, UCI in patients with prelingual bilateral deafness promotes an asymmetric development, which apparently can hardly made undone by the second implant. The maturation of the auditory pathway takes place from the cochlear nerve to the auditory cortex. Both the number of neurons as well as their specificity increase with age. The maturation of the neural auditory system entails myelination, axonal sprouting, axonal diameter increase, development of central dendritic contacts and central synapses and integration of the visual system. This axonal myelination and maturation progresses up to the age of six years.[18] During this sensitive period in which speech and language development takes place, auditory stimulation and perception must occur to organize neural auditory connections. Therefore, auditory input is vital for the maturation of the auditory system.[19] A variety of animal studies have shown that auditory deprivation causes wide-spread degeneration in the central auditory system. Closest to the cochlea, the spiral ganglion cells, the axons of which form the auditory nerve, degenerate progressively when auditory input is not provided.[4,20] The duration of deafness is highly correlated to the extent of degeneration of spiral ganglion cells.[21,22] A study by Sharma et al. examined 104 congenitally deaf children after UCI and found that there is a sensitive period of about 3.5 years during which the human central auditory system remains maximally plastic. After the age of 7, plasticity is greatly reduced. Timing of cochlear implantation is therefore essential in children.

Contrary in adults with postlingually acquired severe to profound SNHL, auditory pathways are already matured. Though, long-term auditory deprivation causes a decline in number and quality of spiral ganglion cells. The time frame of this decline is so long that auditory deprivation up to 10 years is not significantly negatively influencing outcome of cochlear implantation. For that reason, loss of the ability to hear with or without hearing aids more than 10 years prior to inclusion was an exclusion criterion in the RCT. In our RCT, a 2 year inter-implant interval in the seqBiCI group may therefore be too short for auditory deprivation to influence the results negatively. However, when looking at the 3 and 4 year results of this RCT more closely in **Chapter 4** and **Chapter 7,** speech perception in noise and localization of sound results appear to favor simBiCI over seqBiCI, yet not significantly so.

As mentioned in the introduction section, the fundament of binaural hearing is based on three principles: the head shadow effect, the summation effect and the squelch effect.[23,24] The squelch effect refers to the ability of the brain to improve the segregation of incoming speech sound from noise when coming from different directions**.** In **Chapter 5** and **Chapter 6** the squelch effect was calculated for the simBiCI group and the seqBiCI group and differences between groups were noted. The simBiCI group (n=19) could make use of a squelch effect after 2 years of simBiCI, measured for their best performing ear. A squelch effect was measured for both CI ears 3 years after simBiCI.[25] The seqBiCI group, which was smaller (n=16), only showed a squelch effect for the right ear 3 years after seqBiCI. Individuals however could make use of the squelch effect, but proportions were lower compared to the simBiCI group.[26] Numbers are small, hindering statistical analyses in order to explain the difference between groups. Yet, an attempt was made in this thesis. Several possible objective causes for this group difference were assessed but no explanation could be found. This was in contrast to the researchers observations that the majority of participants preferred their first CI. Some of the participants even called the first implanted ear their 'listening ear'. Unfortunately, this observation is not documented in any of the self-reported outcome measures, which again advocates the use of improved (patient related) outcome measures in future cochlear implantation trials. Limitations are of course the small study groups and the fact that power calculations were based on the primary outcome measure: speech perception in noise from straight ahead.

Other factors that are of interest when comparing simBiCI versus seqBiCI are risks of complications and the rehabilitation phase. Complications that occurred during the trial were in line with complications reported in cases of UCI.[27–29] The biggest risk of BiCI is bilateral vestibular dysfunction inducing serious vertigo and instability. For that reason, an electronystagmography was administered to all participants prior to implantation. An advantage of seqBiCI could be that vestibular function is objectified prior to both implantations. One participant in our study experienced vertigo postoperatively in the simBiCI group, whereby vestibular areflexia was excluded as the cause of vertigo.[16] No other participants in the RCT suffered from vertigo. In a cohort study of 168 adults analyzing complications after cochlear implantation, 13 patients suffered from temporary vertigo which resolved in all 13 patients after medical treatment.[28,30,31] As chances of vestibular function loss are low, this should not hinder simBiCI in most cases. Furthermore, the fact that simBiCI necessitates only one phase of rehabilitation can be an importance advocate for this procedure. The rehabilitation phase is characterized by multiple visits to the CI center for hearing evaluations by the speech therapist, adjustments of the CI by the audiologist, and medical check-ups by the otorhinolaryngologist.[32] This factor was not taken into account in our 4 year results. Another former argument for seqBiCI is the anesthetic risk of a long duration of the surgical procedure. In our RCT with postlingually deafened adults, the average age was well over 50 years old. A retrospective cohort study on elderly adults from 2009 found that an increased age itself was no risk factor for complications after cochlear implantation.[33] In the early days of cochlear implantation, UCI surgery could easily take more than 5 hours and anesthetic risks were an argument against simBiCI. Nowadays, with decreasing operation time, the anesthetic risk argument fades to the background. During the RCT, no anesthetic complications occurred in either study group.

The difference in squelch development between simBiCI and seqBiCI may be an indication that on higher order levels simBiCI may hold advantages over seqBiCI. Secondly, for all years of follow-up the results of the simBiCI group were better than the results of the seqBiCI group. After receiving the second CI the seqBiCI group progressed to the level of the simBiCI group. In seqBiCI, this delay in progression of speech perception skills is inherent to the inter-implant interval. The above mentioned nourish a sense of superiority of simBiCI over seqBiCI. As for complications and rehabilitation, no harm of simBiCI compared to seqBiCI is described. Therefore, our advice would be to implant patients with two CIs simultaneously when UCI has not yet taken place.

Tinnitus

Another outcome measures we used in this RCT were two tinnitus questionnaires. As stated in the introduction section, tinnitus is a symptom often experienced in conjunction with hearing loss. Observational studies have shown that cochlear electrical stimulation after implantation can restore hearing abilities but also reduce tinnitus complaints. Yet, in a minority of patients an increase of tinnitus or an induction of tinnitus was reported.[34,35] A systematic review from our research group regarding the effect of cochlear implantation on tinnitus in adult patients with bilateral severe to profound SNHL showed an overall reduction of tinnitus burden after UCI.[34] A meta-analysis was not performed since large heterogeneity existed between studies and few studies were classified as having a low risk of bias. On patient level, the authors found that most studies reported a positive effect of cochlear implantation on tinnitus in the majority of patients. An increase of tinnitus was described in 0-25% of patients as well as newly induction of tinnitus in 0-10% of patients after UCI.

Contrary to UCI, fewer studies reported on the effect of BiCI on tinnitus. To our knowledge only three studies investigated the effect of seqBiCI on tinnitus, of which one is from our research department. Two studies found a positive effect of seqBiCI on tinnitus.[36,37] Olze et al.[36] found a further reduction of tinnitus scores in 28 out of 40 participants (70%) with preoperative tinnitus after receiving the second CI. In a descriptive study from our research department in which the tinnitus results from the RCT were analyzed cross-sectionally based on the TQ and THI questionnaires, we also found an additional benefit of seqBiCI on tinnitus in the majority of patients.[37] Contrarily, an increase of tinnitus scores was found in a study (n=24) by Summerfield et al., due to increased tinnitus in 7 of 16 participants and newly induced tinnitus in 4 of 8 participants without preoperative tinnitus.[38] In **Chapter 7** we evaluated the longitudinal (4 years) tinnitus prevalence outcomes of our RCT comparing simBiCI with seqBiCI. No significant differences in tinnitus prevalence were found between both groups over time.

Cost utility analysis

Today in medical cost-utility studies, uniform quality of life questionnaires are used to measure utility of an intervention. The utility and the costs that derive from the intervention are weighted against each other. In order to decide which interventions to reimburse, a quality adjusted life year (QALY) is calculated per intervention. In the Netherlands a QALY may cost up to 80.000 euro yearly.[39] A cost-utility study from our research department using the 1-year results of this RCT estimated that bilateral implantation becomes cost-effective after a period of 5–10 years CI use based on the Visual Analog Scale (VAS) on hearing and after 10–25 years of CI use based on the time trade-off (TTO) and Health Utilities Index-3 (HUI3).[32,40] This outcome underlines that cost-utility outcome is highly depending on the studied model and used measurement instruments. This was also demonstrated by McRackan et al.[41] who compared general health-related QoL outcome measures and disease-specific/CI-specific outcome measures in unilateral and bilateral cochlear implantation. In the comparison between no CI, unilateral, and bilateral CIs, QoL improvement measured with general health instruments scored much lower compared to improvement in Qol as demonstrated by hearing-specific QoL instruments. The fact that general health-related

QoL outcome measures do not incorporate a hearing element may render them insensitive to the improvements patients notice after cochlear implantation. Given that health-related QoL instruments are used to determine the economic benefit of health interventions, the difference in outcome between these types of instruments suggest that the health economic value of BiCI has been underestimated in previous studies[42–45] which has to be taken into account in the discussion about reimbursement.[41]

CONCLUSIONS

In the first part of this thesis, the results of a retrospective cohort study and a systematic review on prognostic factors in UCI are presented. This thesis underlines that, in adults, age at implantation is not a predictor for post-implant speech perception outcomes. A large part of the variation in post-implant speech perception scores is left unexplained, likely due to the factor of spiral ganglion cells degeneration. In addition, bony disorders such as meningitis and otosclerosis have a negative association with post-implant speech perception scores. When a patient has symmetrical deafness and no factors that favor one ear over the other ear for implantation, we advise to implant the right ear based on a phenomenon called the right ear advantage.

In the second part of this thesis, the results of a RCT are presented on the difference between UCI, simBiCI and seqBiCI. The results underline the clinically relevant benefits of BiCI over UCI on speech perception in noise and localization abilities. Furthermore, this thesis found hints of advantages of simBiCI over seqBiCI, especially on higher order phenomenon called the squelch effect. Our studies on the squelch effect were hindered by small sample sizes and therefore needs corroboration from future studies.

FUTURE RESEARCH

Despite the vast amount of evidence demonstrating advantage of BiCI over UCI, the cost effectiveness of BiCI compared to UCI needs further evaluation. Future studies on this topic should emphasize (hearing related) outcome measures which are highly relevant to the CI candidate in daily life. Furthermore, more research is needed on the development of a squelch effect in patient after simBiCI and seqBiCI using larger numbers of patients and longer follow-up in order to reevaluate the differences we found in the advantage of the simBiCI group. Finally, it is up to the Dutch health care insurance companies to reevaluate the current scientific knowledge on the benefits of BiCI over UCI in order to reconsider reimbursement of bilateral CIs in Dutch adults with bilateral severe to profound hearing loss.

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Chapter 9

Summary

SUMMARY

In **chapter 1** the general introduction of this thesis is presented. The physiology of hearing and pathophysiology of hearing loss are described. The personal and societal impact of hearing loss and tinnitus is touched upon. Since the first successful implantation in the 80s, cochlear implantation has become standard care for patients with severe to profound bilateral sensorineural hearing loss (SNHL). Implantation of a cochlear implant (CI) is invasive and the costs of implantation are high. Therefore, it is valuable to know who will benefit from a CI and who will not. The primary aim of this thesis was to investigate prognostic pre-implant factors in order to predict the post-implant outcome. This way, cochlear implant candidacy and counseling of expected potential benefit of a CI per patient could be improved.

Various observational studies have shown a benefit of bilateral cochlear implantation (BiCI) over unilateral cochlear implantation (UCI) in adults. However, high quality evidence is lacking due to heterogeneity in study populations and outcome measures. In order to gather high-level evidence of the difference between BiCI over UCI, a randomized controlled trial (RCT) was designed in which UCI was compared to BiCI in adult patients with severe to profound SNHL. Thirty-eight participants were randomly allocated to a simultaneous BiCI group (simBiCI) or a sequential BiCI group (seqBiCI) between 2010 and 2012. Participants in the simBiCI group received two CIs in one surgery whereas the participants in the seqBiCI group received two CIs sequentially with an inter-implant interval of 2 years. Follow-up was annually during four years to assess various behavioral and self-reported outcome measures. The study design facilitated comparing objective and subjective outcome of simBiCI versus seqBiCI as well. This thesis describes the 3 and 4 year results of this RCT.

PART 1: UNILATERAL COCHLEAR IMPLANTATION

Outcomes in speech perception following cochlear implantation in adults vary widely. In **chapter 2**, we studied pre-implant factors that influence post-implant speech perception scores in adult patients who were implanted with a unilateral CI. This retrospective cohort study was performed at the University Medical Center Utrecht. A total of 428 adults with bilateral severe to profound SNHL, unilaterally implanted between February 1988 and March 2014, were evaluated. Patients were divided in two groups: prelingually deafened adults and postlingually deafened adults since the outcomes were expected to vary largely between both groups in favor of the postlingually deafened adults based on prior research. Pre-implant factors such as duration of deafness, age at onset of deafness, side of implantation, etiology of deafness, and speech perception scores post-implant where gathered. For the postlingually deafened adult patients, pre-implant speech perception score and age at onset of deafness were found to be positive predictors of post-implant speech perception scores. Meningitis and otosclerosis as cause of deafness were negative predictors of post-implant speech perception scores. For the prelingually deafened adult patients, only the pre-implant speech perception score was a positive predictor of post-implant speech perception scores. Age at implantation was no predictor of post-implant speech perception scores. For both groups, a large proportion of variance in post-implant speech perception was left unexplained by the models created, which is in accordance to previous studies.

A secondary aim of this study was to examine the effect of using multiple imputation for handling missing data at random in a dataset. Multiple imputations is a statistical tool that substitutes randomly missing data by estimated data based on information in the dataset in order to retain the highest statistical power since no data is deleted. In this study, randomly missing post-implant speech perception scores were substituted by scores calculated based on other data in the database. As a result, for example, meningitis was a significant negative predictor for post-implant speech perception scores in the multiple imputation data analysis whereas it was not in the complete case analysis. In conclusion, multiple imputation may assist in overcoming possible bias associated with complete case analysis by maintaining the largest sample size possible.

Although bilaterally deafened subjects benefit from bilateral CIs more than from a single CI with regard to speech perception in noise and localization of sounds, currently the majority of deaf patients is still implanted unilaterally. The selection of ear to be implanted is based on various functional factors such as duration of deafness and anatomical variations. When sensorineural hearing loss is symmetrical, of equal duration on both sides, and when there are no anatomical constraints, it is commonly argued that a CI should be implanted ipsilateral to the patient's dominant hand for easy device use. In **Chapter 3** we reviewed the literature on the effect of side of implantation on unilateral cochlear implant performance in patients with symmetrical severe to profound SNHL. Twelve studies were selected for data extraction of which eleven with a high directness of evidence and a low or moderate risk of bias and one study with a high risk of bias. Pooling of data was impossible since large clinical heterogeneity existed among studies and measures of uncertainty were often not reported. Four of six pediatric studies found a right ear advantage (REA) for one or more outcome measures. Five of eight adult studies found a REA in one or more outcome measures. Handedness did not seem to influence the existence of a REA. Overall, in both prelingually deafened children and postlingually deafened adults, our review of literature showed proof of a REA. Moreover, no studies found proof of a left ear advantage. Based on our systematic review of the literature, we cautiously suggest implanting the right ear in case of symmetrical sensorineural hearing loss in the absence of other prognostic factors favoring one ear for cochlear implantation.

PART 2: BILATERAL COCHLEAR IMPLANTATION

In **chapter 4**, the results are described from the RCT on the difference between outcomes of simBiCI versus seqBiCI. This multicenter RCT is performed in the University Medical Centers of Utrecht, Maastricht, Nijmegen, Leiden and Groningen. Nineteen participants were allocated to be implanted with two CIs simultaneously whereas nineteen other participants were allocated to be implanted with a first CI and two years later with a second CI in the other ear. Follow-up was annually during four years. Behavioral outcome measures were speech perception in noise from straight ahead, speech perception in noise from spatially separated sources, localization of sounds and speech perception in quiet. Self-reported outcome measures were quality of hearing (QoH) questionnaires: the Speech, Spatial and Qualities of Hearing Scale (SSQ), the Nijmegen Cochlear Implant Questionnaire (NCIQ) and the visual analogue scale (VAS) on hearing ability as well as various validated quality of life (QoL) questionnaires: Time Trade Off (TTO), the Health Utilities Index mark 3 (HUI3), the EuroQol five-dimensional questionnaire (EQ-5D) and the VAS on general health. No significant differences were seen between the simBiCI group and the seqBiCI group one year after BiCI for the majority of behavioral and self-reported outcome measures. For the seqBiCI group, speech perception in noise and localization abilities significantly increased after receiving the second CI. Self-reported outcomes (SSQ and social interaction of NCIQ) corroborated the observational results, indicating a clinically relevant benefit of seqBiCI over UCI which is in accordance to previous observational studies. Strikingly, in the simBiCI group the speech perception in noise scores from spatially separated sources test for the better ear continued to increase up to 3 years after implantation. Based on our results, we encourage seqBiCI in adult patients with a unilateral implant in order to optimize speech perception in noise and localization of sound abilities.

In **chapter 5** we investigated whether a squelch effect occurs in the first 3 years after simBiCI. Furthermore we investigated whether this effect increases during follow-up. This was a prospective study as part of the RCT on the difference in outcome between simBiCI versus seqBiCI. Only the nineteen participants from the simBiCI group were evaluated. The squelch effect was evaluated comparing unilateral and bilateral results from the speech perception in noise test from spatially separated sources. In the unilateral condition, the CI at the noise side was turned off. In case the bilateral results were better than the unilateral results, a squelch effect was evident. Patients who underwent simBiCI developed a measurable squelch effect after 2 years in their best performing ear and after 3 years in both ears. These results suggest that after simBiCI the brain learns to segregate speech sound from noise if coming from different directions. An increase was seen over time which suggests a growth in cortical integration and differentiation of inputs from bilateral CIs in time due to brain plasticity.

In **chapter 6** we investigated whether a squelch effect occurs in the first years after seqBiCI as part of the RCT on simBiCI versus seqBiCI. Speech perception in noise from separated sources scores were evaluated in sixteen participants from the seqBiCI group. Since follow-up in the RCT was only two years following seqBiCI, an additional cross-sectional follow-up measurement was performed, a median of 4 years after seqBiCI. Individual patients were able to make use of the squelch effect. However, no significant squelch effect was found on group level, except for the right CI 2 years after seqBiCI. Neither a difference in post-implant performance between the first and second CI ear, nor implanting the better or worse ear firstly could explain the less evident squelch effect in the seqBiCI group compared to the simBiCI group in this study.

In **chapter 7** the four year results are described from the multicenter RCT on simBiCI versus seqBiCI with an inter-implant interval of two years. All four years of follow-up were analyzed longitudinally which enabled us to compare UCI versus BiCI as well as simBiCI versus seqBiCI. Outcome measures entailed the previously mentioned behavioral outcome measures (speech perception in noise from straight ahead, speech perception in noise from spatially separated sources, localization of sounds, and speech perception in quit), three QoH questionnaires (SSQ, NCIQ, and VAS hearing), four QoL questionnaires (TTO, HUI3, EQ-5D, and VAS health), two tinnitus questionnaires (Tinnitus Handicap Inventory and Tinnitus Questionnaire) and complications during the trial. All outcomes were analyzed longitudinally using a linear or logistic regression analysis with an autoregressive residual covariance matrix (generalized estimating equations type). Three participants in the UCI/seqBiCI group did not proceed with their second implantation. During all 4 years of follow-up the UCI/seqBiCI group performed significantly worse compared to the simBiCI group on spatial speech perception in noise in the best performing situation and on all three configurations of localization of sounds. These results were corroborated by the self-reported outcomes, which also showed a significant difference in favor of the simBiCI group for quality of hearing (SSQ, VAS hearing and the NCIQ social interaction subcategory) and in one of the quality of life questionnaires (TTO). The years of unilateral CI use were the cause of the inferior results in the UCI/seqBiCI group indicating a clinically relevant benefit of seqBiCI over UCI. After receiving the second CI, the UCI/seqBiCI group performance did not differ from the simBiCI group performance. Furthermore, no longitudinal differences were seen in tinnitus burden prevalence between groups. Complications that occurred during this trial were infection, dysfunction of the CI, facial nerve palsy, tinnitus and vertigo, which are in accordance to the literature on unilateral cochlear implantation.

In the **general discussion** we summarized the results of this thesis and discussed difficulties and limitations of the current thesis and previous literature. In addition, suggestions were made for future research. The first part of this thesis underlines that, in adults, age at implantation is not a predictor for post-implant speech perception outcomes.

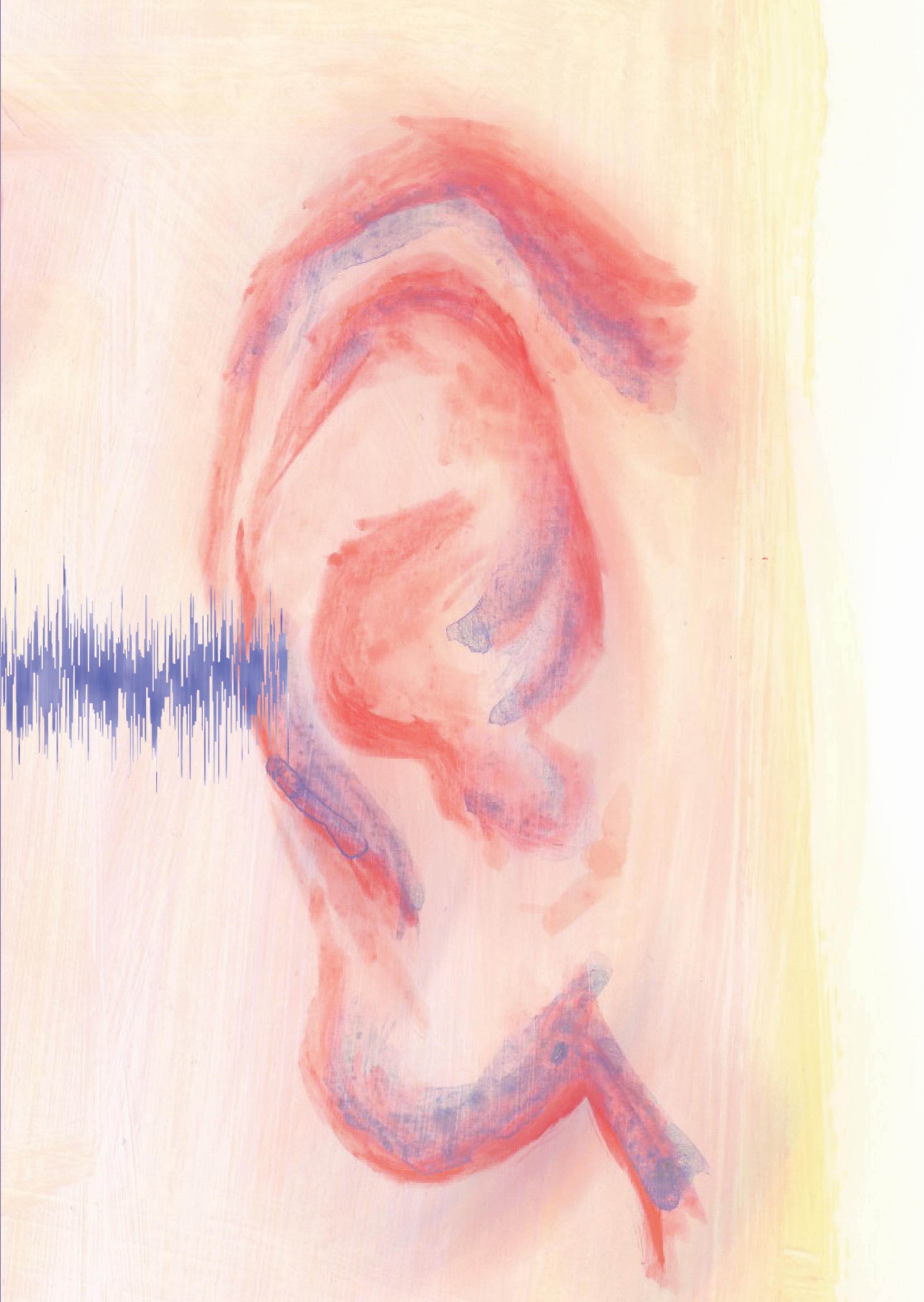
In UCI, when a patient has symmetrical deafness and no factors favoring one ear over the other ear for implantation, we advise to implant the right ear based on a phenomenon called the right ear advantage.

The results of the second part of this thesis underline the clinically relevant benefits of BiCI over UCI on speech perception in noise and localization abilities. Future studies on the cost effectiveness of BiCI should emphasize hearing-related outcome measures which are highly relevant to the CI candidate in daily life. Furthermore, this thesis found hints of advantages of simBiCI over seqBiCI, especially on a phenomenon called the squelch effect. More research is needed on the development of the squelch effect in larger groups of patients after simBiCI and seqBiCI with longer follow-up. Yet, no disadvantages of seqBiCI were seen in our RCT results, opening doors for unilateral CI users to receive a second CI sequentially.

Chapter 10

Summary in Dutch

(Nederlandse samenvatting)



NEDERLANDSE SAMENVATTING

In **Hoofdstuk 1** wordt de algemene introductie van dit proefschrift gepresenteerd. De fysiologie van het gehoor en de pathofysiologie van gehoorverlies en tinnitus worden beschreven. De persoonlijke en maatschappelijke impact van gehoorverlies worden benoemd. Sinds de eerste succesvolle implantatie in de jaren 80, is unilaterale cochleaire implantatie de standaard behandeling geworden voor volwassen patiënten met bilateraal zeer ernstig sensorineuraal gehoorverlies. Cochleaire implantatie is echter invasief en de kosten zijn hoog. Om die reden is het waardevol om te weten wie van een cochleair implantaat (CI) kan profiteren en wie niet. Ons primaire doel was om te onderzoeken welke pre-implantatie factoren een voorspellende waarde hebben op de post-implantatie uitkomst om hiermee indicatiestelling en preoperatieve begeleiding te verbeteren.

Verschillende observationele studies hebben aangetoond dat bilaterale cochleaire implantatie (BiCI) voordelen heeft ten opzichte van unilaterale cochleaire implantatie (UCI). Echter, bewijs van hoge wetenschappelijke kwaliteit ontbreekt als gevolg van heterogeniteit in studie populaties en in uitkomstmaten. Om die reden werd een gerandomiseerde studie opgezet waarin BiCI werd vergeleken met UCI. Achtendertig patiënten werden gerandomiseerd over een simultane BiCI (simBiCI) groep en een sequentiële BiCI groep tussen 2010 en 2012. Patiënten in de simBiCI groep ontvingen twee CIs gedurende één operatie. Patiënten in de seqBiCI groep ontvingen de twee CIs in twee verschillende operaties met een interval van twee jaar. De gehoorresultaten van deze patiënten werden jaarlijks geëvalueerd gedurende vier jaar na (eerste) implantatie. Het studie ontwerp bood ons de mogelijkheid tevens de resultaten van simBiCI versus seqBiCI te vergelijken. Dit proefschrift beschrijft de 3- en 4-jaars resultaten van deze gerandomiseerde studie met als doel de subjectieve en objectieve uitkomsten van beide situaties te evalueren en te vergelijken.

DEEL 1: UNILATERALE COCHLEAIRE IMPLANTATIE

De uitkomsten in spraakverstaan na cochleaire implantatie in volwassenen variëren sterk. In **Hoofdstuk 2** hebben we onderzocht welke pre-implantatie factoren van invloed zijn op post-implantatie uitkomsten in volwassen patiënten met een unilateraal CI. Deze retrospectieve cohort studie werd uitgevoerd in het Universitair Medisch Centrum Utrecht. In totaal werden 428 unilateraal geïmplanteerde patiënten met bilateraal ernstig sensorineuraal gehoorverlies geëvalueerd. De patiënten werden verdeeld in twee groepen: volwassenen prelinguaal dove patiënten en volwassenen postlinguaal dove patiënten vanwege de grote te verwachten verschillen in uitkomst in het nadeel van de prelinguaal dove patiënten op basis van eerdere literatuur. Pre-implantatie factoren zoals duur van doofheid, zijde van implantatie, etiologie van doofheid en post-implantatie spraakverstaan scores werden verzameld. In de volwassen postlinguaal dove patiënten vonden we dat pre-implantatie spraakverstaan scores en leeftijd van ontstaan van doofheid positieve voorspellers waren voor de post-implantatie spraakverstaan scores. Meningitis en otosclerose als oorzaak van de doofheid waren negatieve voorspellers voor de post-implantatie spraakverstaan scores. In de volwassen prelinguaal dove patiënten vonden we dat alleen de pre-implantatie spraakverstaan score een positieve voorspeller was voor de post-implantatie spraakverstaan score. Leeftijd van implantatie was geen voorspeller voor de post-implantatie spraakverstaan scores. Voor beide groepen bleef een groot deel van de variantie in post-implantatie spraakverstaan scores echter onverklaard door ons model. Dit kwam overeen met eerdere studies.

Een secundair doel van deze studie was het onderzoeken van het effect van 'multiple imputation' ter correctie van willekeurig missende data in een dataset. Multiple imputation is een statistische methode waarbij willekeurig missende data in een dataset vervangen worden door geschatte waarden op basis van informatie in de dataset. Missende data worden daardoor niet verwijderd. Hiermee wordt de grootte van de dataset en daarmee de grootst mogelijke statistische power behouden. In deze studie werden willekeurig missende post-implantatie spraakverstaan scores vervangen door geschatte scores op basis van alle overige data in de dataset. Als resultaat van de multiple imputation was meningitis een voorspeller in de multiple imputation analyse terwijl meningitis geen voorspeller was in de analyse waarin missende data verwijderd waren. Op basis van deze studie concludeerden we dat multiple imputation kan helpen in het beperken van bias als gevolg van het verwijderen van willekeurig missende data doordat de grootst mogelijke dataset en daardoor power behouden kan worden.

Alhoewel bilateraal ernstig slechthorende patiënten voordelen ervaren van bilaterale CIs in vergelijking met een unilateraal CI met betrekking tot spraakverstaan in ruis en lokalisatie van geluid, wordt de meerderheid van patiënten nog altijd unilateraal geïmplanteerd. Het selecteren van het te implanteren oor wordt gebaseerd op functionele factoren zoals duur van doofheid en anatomische variatie. Wanneer het gehoorverlies symmetrisch is qua ernst en duur en er geen anatomische bezwaren zijn, wordt er in de regel geïmplanteerd aan de zijde van de dominante hand van patiënt zodat de patiënt het CI gemakkelijk kan bedienen. In **Hoofdstuk 3** hebben we de beschikbare literatuur over het effect van zijde van implantatie op de uitkomst met een unilateraal CI in volwassen patiënten op een systematische manier beoordeeld en samengevat. Twaalf studies werden geselecteerd voor data extractie waarvan elf met een hoge relevantie en een laag of gemiddeld risico op bias en één studie met een hoog risico op bias. Het samenvoegen of 'poolen' van de data was niet mogelijk vanwege de grote klinische heterogeniteit tussen studies en het slecht rapporteren van onzekerheidsmaten bij de uitkomsten. Vier uit zes studies met kinderen vonden een voordeel voor het rechter oor in een of meer uitkomstmaten. Vijf uit acht studies met volwassenen vonden een voordeel voor het rechter oor in een of meer uitkomstmaten. Links of rechtshandigheid had geen invloed op het voordeel voor het rechter oor. Samenvattend, toonde onze systematische beoordeling van de literatuur in zowel prelinguaal dove kinderen als postlinguaal dove volwassenen aanwijzingen van een voordeel voor het rechter oor. Bovendien toonde geen enkele studie een voordeel voor het linker oor. Gebaseerd op de systematische beoordeling van de huidige literatuur adviseren we het rechter oor te implanteren in het geval van symmetrisch sensorineuraal gehoorverlies in afwezigheid van prognostische factoren welke voor implantatie van één van beide oren pleiten.

DEEL 2: BILATERALE COCHLEAIRE IMPLANTATIE

In **Hoofdstuk 4** worden de 3-jaars resultaten beschreven van een gerandomiseerde studie naar het verschil in uitkomst tussen simBiCI en seqBiCI. Deze multicenter studie is uitgevoerd in het Universitair Medisch Centrum Utrecht en patiënten werden geïncludeerd in de Universitair Medische Centra van Utrecht, Maastricht, Nijmegen, Leiden en Groningen. Negentien patiënten kregen twee CIs simultaan terwijl negentien andere patiënten een CI kregen gevolgd door een tweede CI twee jaar later. Uitkomstmaten werden gedurende vier jaar jaarlijks geëvalueerd. Gedragsmatige uitkomstmaten betroffen spraakverstaan in ruis van voren, spraakverstaan in ruis van gescheiden bronnen, lokalisatie van geluid en spraakverstaan in stilte van voren. Zelf gerapporteerde uitkomstmaten waren kwaliteit van horen vragenlijsten: de Speech, Spatial and Qualities of Hearing Scale (SSQ), Nijmegen Cochlear Implant Questionnaire (NCIQ) en de visual analogue scale (VAS) gehoor evenals kwaliteit van leven vragenlijsten: Time Trade Off (TTO), de Health Utilities Index mark 3 (HUI3), de EuroQol five-dimensional vragenlijst (EQ-5D) en de VAS algemene gezondheid. Er werd geen verschil gezien tussen de simBiCI groep en de seqBiCI groep 1 jaar na BiCI voor het merendeel van de gedragsmatige en zelf-gerapporteerde uitkomstmaten. De spraakverstaan scores van de patiënten uit de seqBiCI groep verbeterden significant na het krijgen van het tweede CI. De zelf-gerapporteerde uitkomsten (de SSQ vragenlijst en het 'sociale interactie' domein uit de NCIQ) bevestigden deze verbetering, wat een klinisch relevant voordeel van BiCI ten opzichte van UCI weergeeft. Deze resultaten komen overeen met eerdere observationele studies. De spraakverstaan scores in ruis uit gescheiden bronnen voor het betere oor verbeterden in de drie jaar na simBiCI. Gebaseerd op onze resultaten moedigen we seqBiCI aan in volwassen patiënten met een unilateraal CI zodat het spraakverstaan in ruis en het lokaliseren van geluid geoptimaliseerd kan worden.

In **Hoofstuk 5** onderzochten we of een squelch effect optreedt in de eerste drie jaar na simBiCI. Daarnaast onderzochten we of een squelch effect toeneemt in deze jaren van follow-up. Dit was een prospectieve studie als onderdeel van de gerandomiseerde studie naar de verschillen in uitkomst tussen simBiCI en seqBiCI. Alleen de negentien patiënten in de simBiCI groep werden geëvalueerd. Het squelch effect werd geëvalueerd door de unilaterale en bilaterale spraakverstaan scores in ruis uit gescheiden bronnen te vergelijken. In de unilaterale conditie werd het CI aan de ruis zijde uitgeschakeld. Wanneer de bilaterale score beter was dan de unilaterale score, spraken we van een squelch effect. In de gehele groep werd een squelch effect aangetoond na twee jaar in het beste oor van de patiënt en na drie jaar voor beide oren van de patiënt. Deze resultaten suggereren dat het brein leert om spraak van ruis te onderscheiden wanneer dit uit verschillende richtingen komt. Een toename van het squelch effect gedurende de jaren van follow-up suggereert een toename van corticale integratie en differentiatie van input van bilaterale CIs over tijd als gevolg van brein plasticiteit.

In **Hoofdstuk 6** onderzochten we of een squelch effect optreedt in de jaren na seqBiCI, een prospectieve studie als onderdeel van de gerandomiseerde studie naar de verschillen in uitkomst tussen simBiCI en seqBiCI. Spraakverstaan scores in ruis uit gescheiden bronnen werden geëvalueerd in zestien patiënten uit de seqBiCI groep. Gezien de follow-up slechts twee jaar betrof na seqBiCI, werd een additionele cross-sectionele meting gedaan, mediaan vier jaar na seqBiCI. Op groepsniveau werd geen squelch effect aangetoond behoudens voor het rechter oor twee jaar na seqBiCI. Individuele patiënten toonden wel een squelch effect, alhoewel de proporties lager waren dan in de simBiCI groep. Het zich niet ontwikkelen van het squelch effect in deze groep in tegenstelling tot de simBiCI groep, konden we niet verklaren door een verschil in spraakverstaan met het eerste en tweede CI (dat verschil was er niet), of door het wel of niet als eerste implanteren aan de zijde van het beste of slechtste pre-implantatie oor. Dergelijke statistische analyses zijn lastig door het geringe aantal patiënten in deze groep.

In **Hoofdstuk 7** worden de 4-jaars resultaten beschreven van de gerandomiseerde studie naar simBiCI versus seqBiCI met een interval tussen beide CIs van twee jaar. Alle 4 jaar follow-up werd longitudinaal geanalyseerd wat ons de mogelijkheid bood zowel UCI versus BiCI als simBiCI versus seqBiCI te onderzoeken. Uitkomstmaten waren de eerder genoemde gedragsmatige uitkomstmaten (spraakverstaan in ruis van voren, spraakverstaan in ruis van gescheiden bronnen, lokalisatie van geluid en spraak verstaan in stilte van voren), drie kwaliteit van horen vragenlijsten (SSQ, NCIQ, VAS gehoor), vier kwaliteit van leven vragenlijsten (TTO, HUI3, EQ-5D, VAS gezondheid), twee tinnitus vragenlijsten (Tinnitus Handicap Inventory en Tinnitus Questionnaire) en complicaties. Alle uitkomstmaten werden longitudinaal geanalyseerd met behulp van lineaire of logistische regressie analyse met en autoregressive residual covariance matrix (generalized estimating equations type). Drie patiënten geloot in de UCI/seqBiCI groep werden uiteindelijk niet sequentieel geïmplanteerd. De UCI/seqBiCi groep toonde significant slechtere spraakverstaan in ruis uit gescheiden bronnen scores evenals lokalisatie van geluid scores. Deze resultaten werden bevestigd door de zelf gerapporteerde kwaliteit van horen vragenlijsten (SSQ, VAS gehoor en het 'sociale interactie' domein van de NCIQ). Slechts één van de vier kwaliteit van leven vragenlijsten (TTO) toonde een significant verschil in gemiddelde utiliteit over tijd in het nadeel van de UCI/seqBiCI groep. Hoogstwaarschijnlijk kan het gemiddeld verschil over tijd tussen de groepen verklaard worden door de lagere prestaties van de UCI/seqBiCI groep in hun unilaterale situatie, omdat alle uitkomsten verbeterden tot het niveau van de simBiCI groep na het krijgen van het tweede CI. Met betrekking tot de prevalentie van tinnitus werden er gemiddeld over tijd geen verschillen gezien tussen de groepen. Complicaties die optraden gedurende de studie waren infectie, dysfunctie van het CI, facialis parese, tinnitus en vertigo, welke overeenkomen met de complicaties zoals bekend bij unilaterale cochleaire implantatie.

In de **Algemene discussie** vatten we de resultaten van dit proefschrift samen en bediscussiëren we moeilijkheden en beperkingen van het in dit proefschrift beschreven onderzoek en van dat beschreven in de literatuur. Daarnaast doen we aanbevelingen voor toekomstig onderzoek. Het eerste deel van dit proefschrift onderstreept dat leeftijd van implantatie geen predictor is van post-implantatie spraakverstaan scores in volwassenen. In UCI, bij symmetrisch gehoorverlies zonder factoren welke het ene oor boven het andere oor verkiest, adviseren we het rechter oor te implanteren vanwege een fenomeen genoemd het 'rechter oor voordeel'.

De resultaten van het tweede deel van dit proefschrift onderstrepen de klinisch relevante voordelen van BiCI ten opzichte van UCI op spraakverstaan in ruis en lokalisatie mogelijkheden. Toekomstige studies naar de kosten effectiviteit van BiCI moeten de nadruk leggen op gehoor-gerelateerde uitkomstmaten welke relevant zijn voor CI kandidaten in het dagelijks leven. Daarnaast vonden we in dit proefschrift aanwijzingen voor voordelen van simBiCI ten opzichte van seqBiCI op een uitkomstmaat genoemd het squelch effect. Er is meer onderzoek nodig naar het ontwikkelen van een squelch effect in grotere aantallen patiënten na simBiCI en seqBiCI met een langer vervolg van deze patiënten. Er werden geen nadelen gezien van seqBiCI in onze gerandomiseerde studie. Dit opent deuren voor unilaterale CI gebruikers om een tweede CI te krijgen.

List of abbreviations

AB	Arthur Boothroyd/Advanced Bionics
BiCI	Bilateral cochlear implantation
BIT	Beginners' Intelligibility Test
BPS	Best performance/performing situation
CI(s)	Cochlear implant(s)
CNC	Consonant-nucleus-consonant
CONSORT	Consolidated Standards of Reporting Trials
CSIM	Children's Speech Intelligibility Measure
CUNY	City University of New York
CVC	Consonant-vowel-consonant
dB	decibel
DoD	Duration of deafness
DoE	Directness of evidence
EEG	Electro-encephalography
EQ-5D	EuroQol five Dimensional questionnaire
ERP	Event-related potentials
GFTA	Goldman-Fristoe test of articulation
HA	Hearing aid
HINT	Hearing In Noise Test
HUI3	Health Utilities Index mark 3
IQR	Interquartile range
LIP	Listening progress profile
LOCF	Last observation carried forward
MAIS	Meaningful Auditory Integration Scale
NCIQ	Nijmegen Cochlear Implant Questionnaire
NH	Normal hearing
PCC	Percentage consonant correct
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Ptient related outcome measure
PTA	Pure-tone average
PVC	Percentage vowels correct
QoH	Quality of hearing
QoL	Quality of life
RCT	Randomized controlled trial
REA	Right ear advantage
RoB	Risk of bias
SD	Standard deviation

SeqBiCI	Sequential bilateral cochlear implantation
SimBiCI	Simultaneous bilateral cochlear implantation
SISSS	Speech Intelligibility in noise from Spatially Separated Sources
SNHL	Sensorineural hearing loss
SNR	Signal to noise ratio
SPL	Sound pressure level
SRTn	Speech reception threshold in noise
SSQ	Speech, Spatial and Qualities of hearing Scale
THI	Tinnitus Handicap Inventory
TTO	Time Trade Off
TQ	Tinnitus Questionnaire
UCI	Unilateral cochlear implantation
UMC	University Medical Center
U-STARR	Utrecht-Sentence Test with Adaptive Randomized Roving levels
VAS	Visual analogue scale
WIPI	Word Intelligibility by Picture Identification
WPS	Worst performance/performing situation

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PhD Portfolio

Graduate School of Life Sciences

Name PhD candidate: V.J.C. Kraaijenga
PhD programme: Clinical & Experimental Neuroscience
Date of birth: 14-07-1989
Place of birth: Geldrop
Date thesis defense: 28-11-2019

Educational programme	**# EC**
General courses	
- BROK	1.0
- Techniques and methods in neuroscience (April 2015)	0.5
- Guiding a master student (April 2015)	0.5
- Scientific writing (April 2015)	0.5
- How to make a scientific poster (March 2015)	0.5
- Giving effective oral presentations	1.0
- Academic writing in English	2.0
- Statistics course VUmc	3.6
- Time management (April 2016)	0.5
- Scientific flirting (April 2016)	0.5
- Building your CV (April 2016)	0.5
- Pimp your LinkedIn profile	0.5
- Mindfulness and stress reduction	2.0
- PhD day 2017	0.3
- Team development	0.5
- Writing systematic review	0.5
- Scientific publishing	0.5
Subtotal	**15.4/4.0**
Theoretical / disciplinary courses in broad neuroscience	
- Introduction	0.5
- Summerschool 2015, theoretical part	0.5
- Summerschool 2016, theoretical part	0.5
- Summerschool 2017, theoretical part	0.5
- ONWAR retreat 2016 Woudschoten	1.0
Subtotal	**3.0/2.5**

Courses of other GS-LS PhD programmes and/or attended external courses or meetings

Residency	**6.0**
Scientific presentations on conferences/symposia	
- Otorhinolaryngology twice-annual meeting Nieuwegein 2014	0.6
- Otorhinolaryngology twice-annual meeting Nieuwegein 2015	0.6
- Otorhinolaryngology twice-annual meeting Nieuwegein 2016	0.6
- Otorhinolaryngology twice-annual meeting Nieuwegein 2017	0.6
- Otorhinolaryngology twice-annual meeting Nieuwegein 2018	0.6
- Association of Research in Otolaryngology conference, San Diego CA, USA, February 2016	1.2
- CIAP, 2017, Lake Tahoe, USA	1.2
- Presentation Werkgemeenschap Auditieve Systemen 2017	0.3
- Posterpresentation Science Afternoon Division Surgical Specialties	0.5
- Attendance Werkgemeenschap Auditieve Systemen 2016	0.3
- Attendance Werkgemeenschap Auditieve Systemen 2017	0.3
- Various times during scientific meetings at the ENT department	0.0
Subtotal	**6.8/0.0**

TOTAL NUMBER OF CREDITS (EC) = 31

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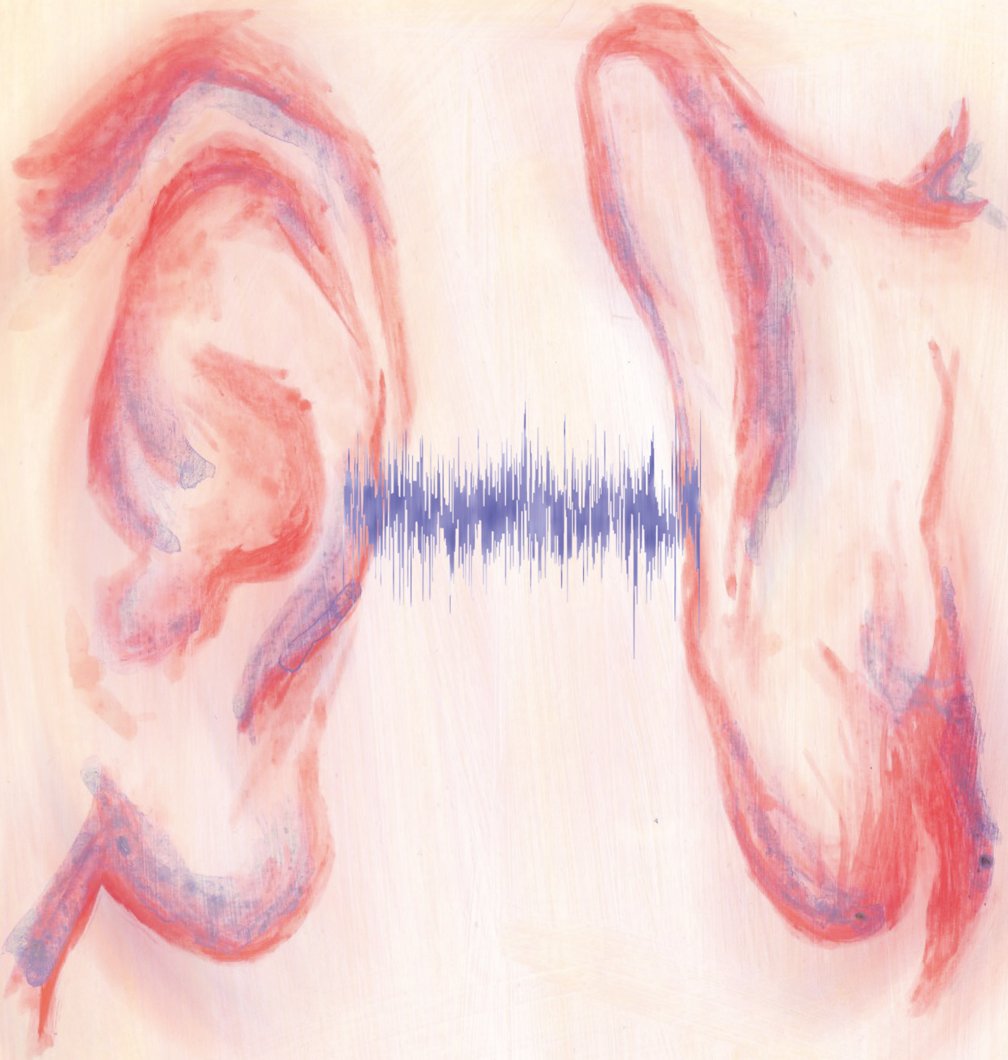
About the author

Véronique Kraaijenga was born on July 14th in Geldrop, the Netherlands, together with her twin sister Charlotte. She grew up with her parents and three sisters in Geldrop (Noord-Brabant). In 2007 she graduated from secondary school and spent a year abroad studying English and Spanish. In 2008 she started her study Medicine at the University of Utrecht. During her medical study she combined her interest in health care and traveling by spending some time in Australia for her clerkship Dermatology (Princess Alexandra Hospital, Brisbane) and some time in Curacao for her clerkship Social Medicine (Wit Gele Kruis, Willemstad). In the final year of her medical study she decided to pursue a career in Otorhinolaryngology and Head & Neck Surgery. She spent six months at the department of Otolaryngology and Head & Neck surgery of the UMC Utrecht for a scientific internship on cochlear implantation (supervised by Dr. A.L. Smit and Prof. dr. W. Grolman) and a clinical internship. After obtaining her Master's degree in 2015, she started as a PhD student at the department of Otorhinolaryngology and Head & Neck Surgery under initial supervision by Prof. dr. W. Grolman and afterwards by Prof. dr. R.J. Stokroos. During her PhD, she gave multiple oral presentations at various (inter)national conferences. In 2018 she started her training in Otorhinolaryngology and Head & Neck surgery in the UMC Utrecht under supervision of drs. I. Ligtenberg-van der Drift and Prof. dr. R.J. Stokroos. During the first years of her residency, she completed part of her training at the St. Antonius Hospital (supervised by dr. M.P. Copper) and the Gelderse Vallei, Ede (supervised by dr. M.H.J.M. Majoor). Véronique lives in Amsterdam together with Yannick van der Weerden. Together they expect to welcome their first child in 2020.



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