UNILATERAL VERSUS SIMULTANEOUS BILATERAL COCHLEAR IMPLANTATION IN ADULTS; A RANDOMIZED CONTROLLED TRIAL

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UNILATERAL VERSUS SIMULTANEOUS BILATERAL COCHLEAR IMPLANTATION IN ADULTS; A RANDOMIZED CONTROLLED TRIAL

Unilaterale versus simultane bilaterale cochleaire implantatie bij postlinguaal dove volwassenen; een gerandomiseerd gecontroleerd onderzoek

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 4 februari 2016 des middags te 2.30 uur

door

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geboren op 21 september 1981 te Helmond

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CONTENT

CHAPTER 01

General introduction

1.1 Physiology of normal hearing

In a normal-functioning ear, sounds travel through the outer ear, middle ear, and are converted to neural information by the inner ear before reaching the brainstem and auditory cortex. The outer ear contains the pinna and external auditory canal, the middle ear includes the tympanic membrane and ossicles (malleus, incus and stapes) and the inner ear consists of the cochlea, labyrinth and auditory nerve (cf. Figure 1). Once sound pressure waves have entered the outer ear, they cause a vibration of the eardrum, ossicles and oval window and cause the perilymph in the scala vestibuli of the cochlea to move (cf. Figure 2). The eardrum and the middle ear facilitate optimal transmission of sound energy from air towards liquid-filled compartments of the cochlea. Inside the cochlea, the basilar membrane oscillates due to perilymph movement, causing a deflection and depolarization of the 3,500 inner hair cells and 12,000 outer hair cells in the organ of Corti (cf. Figure 3). The organ of Corti transduces vibrations into action potentials in the spiral ganglion cells of the auditory nerve that travel to the brainstem and auditory cortex. The basilar membrane moves tonotopically. When stimulated by high frequencies, it mainly moves at the basal entrance, when stimulated by low frequencies at the apex. The ear is an extraordinarily sophisticated organ that enables us to hear frequencies from 20Hz to 20kHz. The high frequency resolution and large dynamic range of 120 dB in both ears enable us to distinguish small directional changes of sounds and to hear the faintest noise to the thunderous sound of a rocket launch [1,2].

1.2 Hearing loss

There are several kinds of hearing loss, dependent on the place of the defect in the auditory system. A conductive hearing loss usually appears when the problem lays within the external auditory canal, the eardrum or middle ear. In case of a pure conductive hearing loss, the fine structures of the inner ear have remained intact and sounds reach the inner ear at a lower sound level only. This means that pure amplification of sounds improves ones hearing, without necessarily reducing the quality. A conductive hearing loss can be treated with surgery, to repair the defect, or with a hearing device. Unfortunately, the most common kind of hearing loss is sensory neural hearing loss, caused by a defect inside the cochlea. When hair cells are damaged, for example due to noise exposure or degeneration, the dynamic range and frequency resolution reduce rapidly. As a result, speech discrimination reduces and patients are no longer able to

reach a 100% speech understanding level, even if presented at a high sound level or with the best hearing aids. In case of a relatively limited sensory neural hearing loss, hearing aids are the first treatment option. Although hearing aid technology improves continuously, they will never be able to replace the sophisticated fine structure and function of thousands of hair cells.

1.3 Binaural hearing

Having two ears enables us to differentiate sounds of interest from background noise and locate where sounds come from, which are both everyday listening situations. For this, we utilize the following effects [5-8]:

1. Sounds from a source outside the midplane of the head travel further to the farther ear, which causes inter aural time differences (ITDs) between the ears. The brain uses these differences to determine the direction of sounds with frequencies below about 1500 Hz in the horizontal plane.
2. The farther ear is in the head's shadow for the sound source. This causes inter aural level differences (ILDs) for sounds with frequencies above about 1500 Hz: the head acts as a sound barrier and attenuates sounds on the side contralateral to the signal.
3. We can determine the direction of a sound source by combining ITD and ILD information.
4. When listening in daily life, we turn one ear (a little or totally) to the source of interest (speech for example) and create head shadow for interfering other sound sources (noise). We can focus on the ear with the better signal-to-noise ratio (SNR) and understand speech even if the noise is much louder than the speech.
5. Binaural squelch effect: the brain can improve speech perception further by not only focusing on the ear in the head shadow, but also by suppressing the noise signals in this ear.
6. Binaural summation: When identical signals are presented to the two ears, the brain uses binaural redundancy and binaural loudness summation to distinguish sound of interest from noise.

The above-mentioned effects cannot be fully repaired by the use of hearing aids. The most-heard complaint of hearing aid users is that they have difficulties with

Figure 1 | The hearing organ [3]

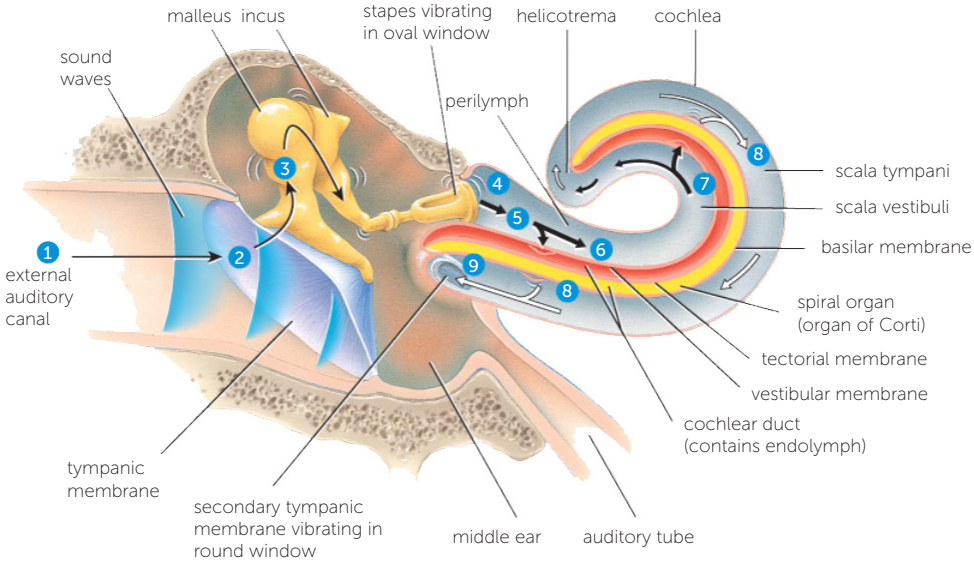

Figure 2 | The inner ear [4]

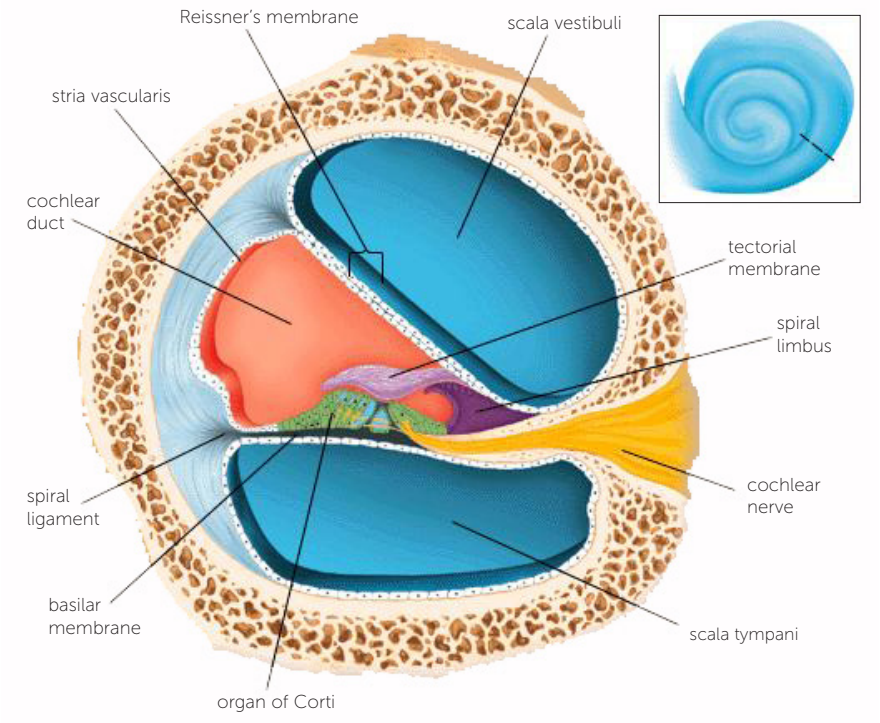

Figure 3 | The organ of Corti [4]

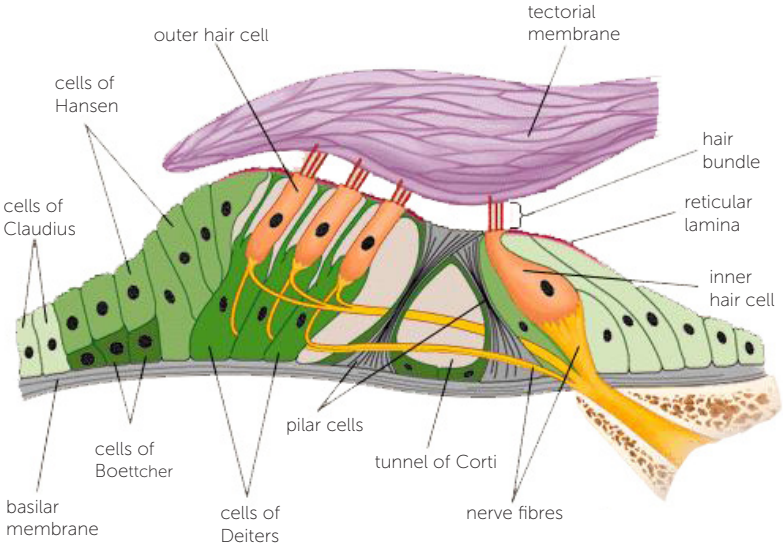

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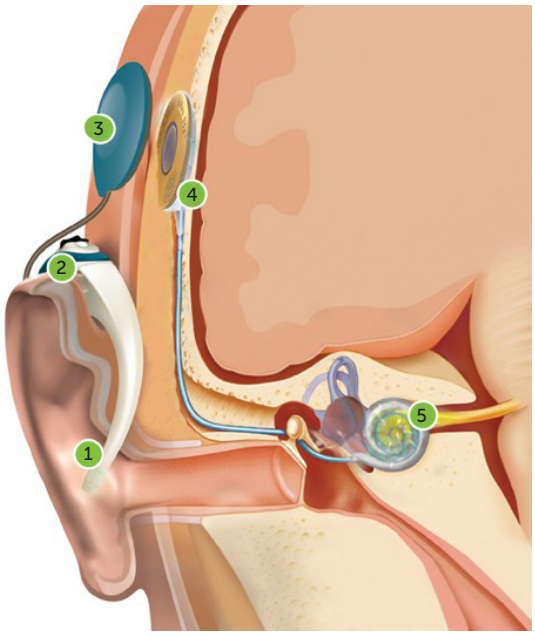
Figure 4 | Advanced Bionics ® Cochlear implant [10]



1. The microphone captures sound waves. 2. The external speech processor converts sound into digital signals. 3. The magnetic headpiece sends the signals to the internal implant. 4. The internal implant converts the digital signals into electrical energy, sending it to: 5. The electrode array inside the cochlea; the electrodes stimulate the auditory nerve.

understanding speech in background noise. Also, they are less able to localize sounds of interest. A decreased dynamic range is another problem frequently reported; sound is either too loud or not loud enough.

1.4 Reimbursement of hearing aids

Until 3 years ago, insurance companies in the Netherlands only reimbursed a hearing aid if the hearing loss in the **best** hearing ear was at least 35dB. This meant that patients with a unilateral hearing loss did not receive a reimbursement. In case of a substantial unilateral loss, this had a large effect on their spatial listening capabilities. In 2012, rules changed and a hearing aid is now reimbursed, even if a person has one well-functioning ear.

Table 1 | WHO grades of hearing impairment [9]

Grade of impairment	Corresponding audiometric ISO value	Performance
0 - No impairment (better ear)	25 dB or better	No or very slight hearing problems. Able to hear whispers.
1 - Slight impairment (better ear)	26-40 dB	Able to hear and repeat words spoken in normal voice at 1 metre.
2 - Moderate impairment (better ear)	41-60 dB	Able to hear and repeat words spoken in raised voice at 1 metre.
3 - Severe impairment (better ear)	61-80 dB	Able to hear some words when shouted into better ear.
4 - Profound impairment including deafness (better ear)	81 dB or greater	Unable to hear and understand even a shouted voice.

Grades 2, 3 and 4 are classified as disabling hearing impairment.
The audiometric ISO values are averages of values at 500, 1000, 2000, 4000 Hz.

1.5 Cochlear Implantation (CI)

Hearing loss can be categorized into 5 grades: no impairment, slight, moderate, severe or profound impairment (including deafness) (cf. Table 1). In case of severe to profound hearing impairment, hearing aids may be inadequate and cochlear implants may be considered. In addition, in the Netherlands, a cochlear implant is usually provided

when the speech perception score in silence, with the best fitted hearing aids, is 50% or less at 65dB SPL (65dB sound pressure level (SPL) is normal conversational speech level). A cochlear implant consists of an external part: a microphone, speech processor and transmitter, and an internal part: a receiver and electrode array. The latter parts are surgically implanted underneath the temporal muscle and inserted within the cochlea respectively (cf. Figure 4).

A cochlear implant receives sound, processes it, transmits and converts it into electrical signals, and presents it to the brain by direct stimulation of the spiral ganglion cells (SGCs) in the auditory nerve. CI has proven to be very successful since its introduction in the nineteen seventies. This mainly applies to patients in whom the central auditory pathways have developed, i.e. in those who received an implant at an early age or who lost their hearing later in life, after auditory cortex development [11].

1.6 The societal impact of hearing loss

Worldwide, over 550 million people suffer from disabling hearing loss (≥35dB in the better ear) of which over 60 million suffer from severe hearing loss or worse (≥61dB) [12]. 10% of the people in our Western population suffer from moderate to profound hearing loss. In the Netherlands, 1.4 million adults have some kind of hearing loss. In 2007, the national total societal costs for the diagnosis "hearing impairment" were estimated to be 711 million euros, which is about 1% of the total health care costs (74.4 billion euros) [13].

1.7 Reimbursement of CI

In our country, adult patients eligible for CI, normally receive reimbursement for one cochlear implant only. Cochlear implantees are, overall, severely to profoundly deaf in both ears and after receiving a cochlear implant, they still have a significant hearing impairment. As we described above, people who can be fitted with hearing aids, already encounter serious problems in difficult listening situations, let alone cochlear implant users who are provided with one implant, but still have a deaf ear on the other side.

There is an ongoing discussion in the Netherlands on whether or not bilateral CI (BiCI) should be provided as standard care for adults, as it is in Germany and Scandinavia [14]. In November 2006, the *College voor Zorgverzekeringen* (CVZ) (now *Zorg instituut Nederland, ZiNL*) advised Dutch health insurance companies to reimburse BiCI only in case of post meningitis hearing loss for both adults and children [15]. The reason for this was

that meningitis might lead to ossification of the cochlea, which may make CI later in life impossible.

Between 2009 and 2012 several studies were published that demonstrated that BiCI in prelingually deafened children until the age of 5, had a positive effect on speech and language development. Literature also showed that speech understanding in noise and the capability to localize sounds significantly improved due to BiCI [14]. Based on these findings, CVZ (ZiNL) concluded that there was enough evidence to justify the reimbursement of a second implant in children, until the age of 5 years [16].
Several authors have reviewed the literature on the benefits of BiCI compared to unilateral CI (UCI) in adults [17-19]. Although they demonstrated that bilateral implants are beneficial for speech perception in noise (especially when speech and noise are presented from different directions) [20-23], for localization of sounds [24-29], and improvement of quality of hearing and quality of life [20,22,24,25], they concluded that the majority of studies had a low level of evidence and that there was a lack of well-performed randomized studies with low chance of bias, sufficient amounts of patients, and a representative duration of follow-up for an indisputable answer on this matter [17-19]. For this reason, ZiNL concluded in 2012 that reimbursement of a second cochlear implant could not be justified for older children and adults [16].

1.8 Aims and outline of this thesis

In order to properly investigate the benefits and cost-utility of BiCI compared to UCI, in adults with severe bilateral postlingual hearing loss, we started a multicenter, randomized controlled trial (RCT) in 2010. Thirty-eight patients were included in this study. Nineteen patients received two cochlear implants simultaneously. The other 19 patients first received one cochlear implant and a second implant 2 years later. All participants were followed up for 4 years and we tested their spatial listening capabilities, quality of life and quality of hearing on a yearly basis. In order to adequately test the participants' spatial listening capabilities, we used the AB-York crescent of sound [29]. This test setup was created for this study and had not been used on Dutch patients before. The setup contains several hearing tests. The primary outcome measure of our study was speech understanding in noise, with speech and noise coming from straight ahead. Speech-in-noise-understanding was tested with the U-STARR (Utrecht Sentence Test At Randomized Roving levels). **Chapter 2** describes the validation of the

U-STARR conducted with the AB-York Crescent of Sound. In **Chapter 3**, we present the answer to the first major objective of this thesis: the effectiveness of simultaneous bilateral cochlear implantation compared to unilateral cochlear implantation after a follow-up of 1 year. In **chapter 4**, we answer the second major question and performed cost–utility analyses for bilateral versus unilateral cochlear implantation. In **chapter 5**, we compare the subjective and objective results of the study participants. Did the questionnaire results correspond with the results we found with the objective hearing tests? Chapters 3 and 4 show the benefits of simultaneous BiCI compared to UCI in postlingually deafened adults. When the study proceeds, we will also be able to show the differences between simultaneous bilateral implantation and sequential bilateral implantation. In order to be able to decide which unilateral cochlear implantees should benefit from a second implant, it is useful to know what the effect of time between implantations is on hearing performance. **Chapter 6** describes a systematic review in which the literature on this topic is discussed. **Chapter 7** is a discussion of the preceding chapters.

REFERENCES

1. Hudspeth AJ. Integrating the active process of hair cells with cochlear function. *Nat Rev Neurosci.* 2014 Sep;15(9):600-14. doi: 10.1038/nrn3786. Epub 2014 Aug 6.

2. Lamoré PJJ, Prijs VF, Franck BAM. "Eigenschappen gehoor. " *Nederlands Leerboek Audiologie*. Nederlandse Vereniging voor Audiologie, 2000. Web. 1 September 2015. www.audiologieboek.nl.

3. Aulner. "Ch 17 The special senses Deck." *Biology 223*. Study Blue, College of Southern Nevada, 2015. Web 2 September 2015. www.studyblue.com/notes/note/n/ch-17--the-special-senses deck/deck/13028964.

4. Hawkins JE. *Human ear.* Encyclopaedia Britannica, Inc. 1997. Web 28 August 2015. http://www.britannica.com/science/ear.

5. Middlebrooks JC, Green DM. Sound localization by human listeners. *Ann Rev Psychol* 1991;42:135-59.

6. Bronkhorst AW, Plomp R. The effect of head-induced interaural time and level differences on speech intelligibility in noise. *J Acoust Soc Am* 1988;83:1508-16.

7. Dirks DD, Wilson RH. The effect of spatially separated sound sources on speech intelligibility. *J Speech Hear Res* 1969;12:5-38.

8. MacKeith NW, Coles RRA. Binaural advantages in hearing of speech. *J Laryngol Otol* 1971; 85:213-32.

9. World Health Organization. "Grades of hearing impairment". *Prevention of blindness and deafness*. World Health Organization, 2015. Web 27 August 2015. http://www.who.int/pbd/deafness/hearing_impairment_grades/en/.

10. Advanced Bionics. *"How hearing with a cochlear implant system works."* Choose to you're your best with cochlear implants. Advanced Bionics 2015. Web 1 September 2015. http://www.advancedbionics.com/com/en/your_journey/what_is_a_cochlearimplantsystem.html.

11. Sharma A, Dorman MF, Spahr AJ. A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear Hear* 2002;23:532–9.

12. Stevens G, Flaxman S, Brunskill E, Mascarenhas M, Mathers CD, Finucane M. Global Burden of Disease Hearing Loss Expert Group. Global and regional hearing impairment prevalence: an analysis of 42 studies in 29 countries. *Eur J Pub Health* 2013;23(1):146-52.

13. van Thiel L. *TNS NIPO rapport* Gehoor Nederland 2010.

14. CI-ON (Cochleaire Implantatie Overleg Nederland) 19 december 2012. Richtlijn indicatie bilaterale cochleaire implantatie voor kinderen van 5 tot en met 18 jaar. *In English: CI-ON (Dutch cochlear implantation group) 19 December 2012. Guideline indication bilateral cochlear implantation in children of 5-18 years of age.*

15. College voor Zorgverzekeringen. Implantatie van een tweede cochleair implantaat is alleen aangewezen bij

postmeningitis doofheid. CVZ 2006. http://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/rapporten-en-standpunten/2006/0611-implantatie-van-een-tweede-cochleair-implantaat-is-alleen-aangewezen-bij-postmeningitis-doofheid/0611-implantatie-van-een-twe.

16. Van Eijndhoven MJA., Gaasbeek Janzen MH, Heymans J. Herbeoordeling standpunt bilaterale cochleaire implantaten bij kinderen. College voor Zorgverzekeringen, Diemen 2012.

17. Ramsden R, Greenham P, O'Driscoll M, et al. Evaluation of bilaterally implanted adult subjects with the Nucleus 24 cochlear implant system. *Otol Neurotol* 2005;26:988-98.

18. Ricketts TA, Grantham DW, Ashmead DH, Haynes DS, Labadie RF. Speech recognition for unilateral and bilateral cochlear implant modes in the presence of uncorrelated noise sources. *Ear Hear* 2006;27:736-73.

19. Dunn CC, Noble W, Tyler RS, Kordus M, Gantz BJ, Ji H. Bilateral and Unilateral Cochlear Implant Users Compared on Speech Perception in Noise. *Ear Hear* 2010;31:296-8.

20. Laszig R, Aschendorff A, O'Driscoll M, et al. Benefits of bilateral electrical stimulation with the nucleus cochlear implant in adults: 6-month postoperative results. *Otol Neurotol* 2004;25:958-68.

21. Litovsky R, Parkinson A, Arcaroli J, Sammeth C. Simultaneous bilateral cochlear implantation in adults: a multicenter clinical study. *Ear Hear* 2006;27:714-31.

22. Dunn CC, Tyler RS, Oakley S, Gantz BJ, Noble W. Comparison of speech recognition and localization performance in bilateral and unilateral cochlear implant users matched on duration of deafness and age at implantation. *Ear Hear* 2008;29:352-9.

23. Neuman AC, Haravon A, Sislian N, Waltzman SB. Sound-direction identification with bilateral cochlear implants. *Ear Hear* 2007;28:73-82.

24. Noble W, Tyler R, Dunn C, Bhullar N. Unilateral and bilateral cochlear implants and the implant-plus-hearing-aid profile: comparing self-assessed and measured abilities. *Int J Audiol* 2008b;47:505-14.

25. Grantham DW, Ashmead DH, Ricketts TA, Labadie RF, Haynes DS. Horizontal-plane localization of noise and speech signals by postlingually deafened adults fitted with bilateral cochlear implants. *Ear Hear* 2007;28:524-41.

26. Noble W, Tyler RS, Dunn CC, Bhullar N. Younger- and Older-Age Adults With Unilateral and Bilateral Cochlear Implants: Speech and Spatial Hearing Self-Ratings and Performance. *Otol Neurotol* 2009;30:921-9.

27. Litovsky RY, Parkinson A, Arcaroli J. Spatial Hearing and Speech Intelligibility in Bilateral Cochlear Implant Users. *Ear Hear* 2009;30:419-31.

28. Noble W, Tyler R, Dunn C, Bhullar N. Hearing handicap ratings among different profiles of adult cochlear implant users. *Ear Hear* 2008a;29:112-20.

29. Kitterick PT, Lovett RES, Goman AM, Summerfield AQ. The AB-York crescent of sound: an apparatus for assessing spatial-listening skills in children and adults. Cochlear Implants Int 2011;12(3):164-9.

CHAPTER 02

Validation of the U-STARR with the AB-York Crescent of Sound, a New Instrument to Evaluate Speech Intelligibility in Noise and Spatial Hearing Skills

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ABSTRACT

The Advanced Bionics ® (AB)-York crescent of sound is a new test setup that comprises speech intelligibility in noise and localization tests that represent everyday listening situations. One of its tests is the Sentence Test with Adaptive Randomized Roving levels (STARR) with sentences and noise both presented from straight ahead. For the Dutch population, we adopted the AB- York setup and replaced the English sentences with a validated set of Dutch sentences. The Dutch version of the STARR is called the Utrecht-STARR (U-STARR). This study primarily assesses the validity and reliability of the U-STARR compared to the Plomp test, which is the current Dutch gold standard for speech-in-noise testing. The outcome of both tests is a speech reception threshold in noise (SRTn). Secondary outcomes are the SRTn measured with sounds from spatially separated sources (SISSS) as well as sound localization capability. We tested 29 normal-hearing adults and 18 postlingually deafened adult patients with unilateral cochlear implants (CIs). This study shows that the U-STARR is adequate and reliable and seems better suited for severely hearing-impaired persons than the conventional Plomp test. Further, CI patients have poor spatial listening skills, as demonstrated with the AB-York test.

INTRODUCTION

Cochlear implantation is a successful way to restore auditory communication in severely hearing-impaired persons. Although cochlear implant (CI) patients generally hear well in a quiet setting, hearing with background noise, as is normal in daily practice, remains challenging [1,2,3]. The evaluation of spatial hearing and hearing-in-noise capabilities becomes increasingly important in this era of improving sound processing strategies, implantation techniques, and a growing interest in bilateral implantation. Traditional speech tests comprise words or sentences presented at fixed levels, and cochlear implantees are often allowed to adjust their processor volumes. These tests are not representative of everyday listening situations, in which levels of speech and background noise change constantly. In 1979, Plomp and Mimpen developed a Dutch hearing-in-noise test for people with difficulties understanding speech in background noise but with relatively good pure tone audiometry (PTA) thresholds. In this test, sentences are presented at a level at which a person can understand the words in silence, after which noise is added in an adaptive manner. A sentence is scored as correct when repeated 100% correctly. The outcome is a speech reception threshold in noise (SRTn), defined as the signal-to-noise ratio (SNR) at which the person is able to repeat 50% of the sentences correctly [4]. Although this test is useful for people with relatively good hearing, it is too difficult for CI patients [5]. Even in silence, it is difficult for CI patients to reproduce sentences 100% correctly, which would result in poor Plomp test results. These patients are, however, usually good at understanding speech by using the context of words. Recently, the clinical research department of Advanced Bionics ® developed the Sentence Test with Adaptive Randomized Roving levels (STARR). In this test, sentences are presented in noise, and the number of key words correctly repeated per sentence is scored instead of whole sentences correctly repeated [6,7,8]. This seems more suitable for CI patients than the original, difficult Plomp test. In the STARR, CI patients are allowed to make small mistakes while they can still show that they have understood the sentence. In collaboration with Advanced Bionics, Prof. Q. Summerfield's research group in York developed a new test setup that enables the presentation of the STARR sentences in noise – at roving levels and from different directions [7]. We have adopted this Advanced Bionics (AB)-York crescent of sound test setup for the Dutch population and replaced the English STARR material with a validated set of Dutch sentences (the VU98 list of sentences, recorded by a female

speaker [9]). This new Dutch speech-in-noise test is called the Utrecht-STARR (U-STARR). The main goals of this study were (1) to validate the U-STARR by measuring a group of normal-hearing persons, (2) to test the reliability of the U-STARR compared to the conventional Dutch Plomp test in normal-hearing persons and CI patients, and (3) to test our hypothesis that the U-STARR is better suited for CI patients than the Plomp test. Secondary outcomes were speech intelligibility in noise with sounds coming from spatially separated sources (SISSS) as well as sound localization capabilities, both evaluated with this new setup.

Subjects and Methods

This cross-sectional study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Human Ethics Committee of the University of Utrecht (NL2499001808).

Subjects

Twenty-nine normal-hearing adults were recruited by means of advertisements posted at the otolaryngology outpatient clinic of the University Medical Center Utrecht, and 18 CI patients were selected through the hospital CI database. They all met the inclusion criteria outlined in table 1 and were enrolled in the study after they gave written informed consent.

Table 1 | Inclusion criteria

Normal hearing group	CI patients
Age ≥ 18 and ≤ 70 years	Age ≥ 18 and ≤ 70 years
PTA ≤ 20dB HL at 500-4000 Hz	Post-lingual onset of hearing loss defined as: the patient attended mainstream education
Speech intelligibility threshold ≥ 95% at 50dB SPL	At least one year of CI experience
Dutch language proficiency	Dutch language proficiency
Willingness and ability to participate in all scheduled procedures	Willingness and ability to participate in all scheduled procedures

PTA= Pure Tone Audiometry

In order to get a homogenous group of CI patients, we selected participants in whom the auditory cortex had developed in early life (i.e. postlingually deafened). Since it is often difficult to accurately determine at which age a severe hearing loss started, we used the criterion of all participants having attended mainstream education. Even if the patients used hearing aids in class, their auditory cortex would have developed well enough to consider them postlingually deafened. Furthermore, in the Netherlands, it is very unlikely that a deaf or severely hearing-impaired child would be placed in mainstream education. All participants knew exactly which type of education they had followed. Further details on the participants are presented in table 2.

The Dutch AB-York Crescent of Sound Test Setup

Speech intelligibility in noise and sound localization tests were conducted in a soundproof room with 9 audiovisual stands in the frontal hemifield. Seven of these stands were positioned at 30- degree intervals, and 2 additional stands were positioned at 15-degree intervals on either side of 0°. The audiovisual stands were positioned in a crescent shape with a radius of 1.45 m and extended to a height of 1.1 m (cf. Figure 1) [7]. The original AB-York test setup contains English sentences. We replaced these sentences by the Dutch VU98 sentences, a set of 39 lists, each comprising 13 sentences [9]. This large and validated set, recorded by a female speaker, is not being used for other hearing evaluation purposes in our department. The sentences were therefore new to all patients.

Test Procedure

Baseline Hearing Tests

The hearing of normal-hearing persons was tested with a standard PTA and a Dutch phoneme test (consonant-vowel-consonant or CVC test). In the CI group, the phoneme test was conducted in three listening conditions: monaurally, with either the CI or the hearing aid switched on, and bimodally, with both the CI and the hearing aid switched on.

Dutch AB-York Crescent of Sound

The test battery conducted with the Dutch AB-York crescent of sound consisted of a Plomp test, the U-STARR, a SISSS, and a sound localization test. In the Plomp test, sentences and noise were both presented from straight ahead. A sentence was scored

Table 2 | Patient characteristics

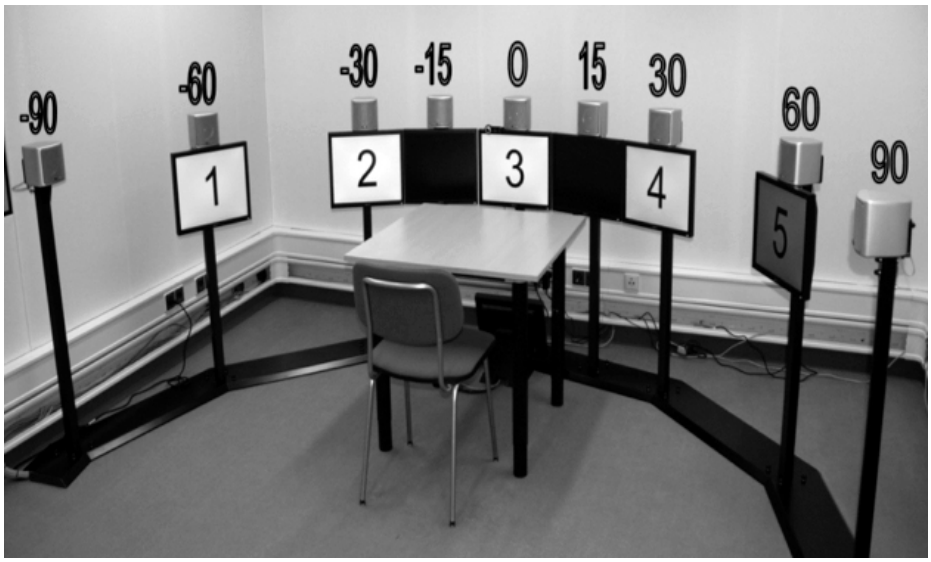
	CI patients (n=18)		Normal hearing controls (n=29)	
	n (%)	Mean (SD)	n (%)	Mean (SD)
Gender				
Male	7 (38)		13 (45)	
Female	11 (62)		16 (55)	
Age at Test moment (yrs)		55.6 (11.9)		37.1 (13.3)
Age at onset hearing loss (yrs)		25.6 (15.8)		
Age at implantation (yrs)		50.4 (11.7)		
CI Brand & type				
Cochlear Nucleus CI 24R	2 (11)			
Cochlear Nucleus CI 22M	1 (6)			
Cochlear Nucleus CI 24M	1 (6)			
Cochlear Nucleus CI 24RE	1 (6)			
MedEl Sonata	1 (6)			
Advanced Bionics HiRes 90K	12 (67)			
Implanted side				
Left	10 (56)			
Right	8 (44)			
Hearing aid use				
Yes	12 (67)			
No	6 (33)			
Hearing capabilities				
PTA right				4.8 (4.9)
PTA left				4.3 (5.2)
Speech intelligibility at 65dB HL (%)				
CI only (n=18)		70 (12.2)		
CI+HA (n=12)		74 (13.5)		

CI = Cochlear Implant, HA = Hearing aid, PTA = Pure Tone Audiometry

as correctly repeated when all words were repeated correctly. The outcome was the SNR necessary to repeat 50% of the sentences correctly; this is the SRTn (in dB) 4. In the U-STARR, sentences and noise were also presented from straight ahead, but the number of key words repeated correctly was scored instead of whole sentences. Two researchers and a speech therapist independently selected the key words per sentence and debated on their differences to make a final selection. Five key words were selected

in long sentences and 3 key words in shorter sentences. In the U-STARR, a sentence was scored as correctly repeated when a subject repeated at least 3 out of 5 or 2 out of 3 key words correctly. As in the Plomp test, the U-STARR result was the SRTn. In both the Plomp test and the U-STARR, sentences were presented at 65, 70, or 75 dB SPL (randomly selected) with an initial SNR of +20 dB (sentence 20 dB louder than noise). The noise started 500 ms before and continued 500 ms after the sentence. The SNR was measured with an adaptive procedure: if a sentence was scored as correct, the SNR for the next sentence was decreased by increasing the level of noise (compared to the sentence), and the task became more difficult. If the sentence was scored as incorrect, the SNR for the next sentence was increased by decreasing the level of noise, thus making the task easier. In the first phase, the SNR was reduced in 10-dB steps following a correct response or increased in 10-dB steps following an incorrect response. In phases 2 and 3, steps of 5 and 2.5 dB were used, respectively. The last step was used for the remainder of the sentences. The SNR average of the last 10 sentences in the list was calculated, which resulted in the SRTn. For testing SISSS, the same procedure was used as for the U-STARR. The only difference was that the sentences were presented from 60° to the left (–60° azimuth) or to the right (+60° azimuth) of the subject, and the noise was presented from 60° on the opposite side (cf. Figure 1). In the sound localization test, numbers appeared on the screens under the loudspeakers at 0-, ±15-, ±30-, and ±60-degree angles. The phrase 'Hello what's this?' was randomly presented from one of the loudspeakers above the screens, 30 times in total, at 60, 65, or 70 dB SPL (roving levels). First, the sentence was presented from –60, 0, and +60°. The result was calculated as the percentage of correct responses with a 60-degree angle between loudspeakers. Second, the test was performed with loudspeakers at –60, –30, 0, +30, and +60° to determine the percentage correct with a 30-degree angle between loudspeakers. Lastly, the sentence was presented from loudspeakers at –30, –15, 0, 15, and 30° to determine the percentage correct with a 15-degree angle between loudspeakers. Again, in the CI group, all tests were performed in three listening conditions: monaurally, with either the CI or the hearing aid switched on, and bimodally, with both the CI and the hearing aid switched on. The participants were instructed to face the loudspeaker positioned straight ahead of them and not to turn their head during the tests. The tests were conducted by 3 individuals according to the protocol.

Figure 1 | AB-York crescent of sound, test setup



Repeated Measures

In order to compare the reliability of the Plomp test and the U-STARR, we repeated these tests on separate days in 12 normal-hearing persons. The VU98 set of sentences is large enough to prevent presenting the same sentence twice.

Statistical Analysis

The data were gathered in Microsoft Excel, and SPSS 20 was used for the statistical analysis. Measures of the ability to understand speech in noise were compared within and between groups with a paired t-test or with Student's t-test, respectively. The differences were calculated with 95% confidence intervals. For SISSS testing, subjects usually had one presentation condition in which they performed better than in the other. We compared the results for the best performance condition in the CI group with those for the best performance condition in the normal-hearing group. We also compared the worst performance condition in the same manner.

In the localization test, it was possible to choose the correct source by chance without actually hearing it well, because subjects were asked to choose from a fixed set of options. In order to examine whether subjects performed better (or worse) than at chance level, we used the Wilcoxon signed-rank test.

Sample Size Analysis

The primary outcome was the SRTn measured with the U-STARR as compared to that measured with the Plomp test. For the power analysis, we used test results of the normal hearing subjects on the conventional Plomp test and the English STARR, as described in the literature. On the conventional Plomp test, a mean of –7.3 dB (SD 1.0) was found by Plomp and Mimpen when 10 normal-hearing listeners were tested [4]. Boyle et al. performed the STARR in 25 normal-hearing adults and found a mean SRTn of –5.9 dB (SD 1.3) [8]. To detect a clinically relevant difference of 1.4 dB in SNR between the two tests, with an α of 0.05, a power of 80%, and an SD of 1.2 dB, $\geq$ 6 subjects per group would be sufficient.

Results

Subjects

Twenty-nine normal-hearing subjects participated in this study. Their mean age was 37 years (range 20–66). Their average PTA was 4.8 dB (range –2 to 18) on the right side and 4.3 dB (range –2 to 17) on the left. They all reached 100% speech intelligibility, on average at 51 $\pm$ 12.1 dB HL (range 40–70). Eighteen unilaterally implanted patients participated. Their mean age was 56 years (range 31–70). On average, their hearing impairment started at the age of 26 years (range 2–55), and they were implanted at 50 years of age (range 27–67). The average speech intelligibility at 65 dB HL was 70% (range 50–87) (cf. Table 2).

Speech Intelligibility in Noise

In the normal-hearing group, the mean SRTn values of the U-STARR and the Plomp test were –5.6 dB (SD 1.2) and –3.7 dB (SD 1.5), respectively (cf. Table 3). The difference was statistically significant ($p < 0.01$) due to small variances. In the CI group, the mean SRTn of the U-STARR, when only the CI was switched on, was 9.9 dB (SD 4.2) and differed significantly from the mean SRTn of the Plomp test, which was 15.1 dB (SD 7.0; $p < 0.01$). Twelve out of the 18 implanted subjects used a contralateral hearing aid. When both the CI and the hearing aid were switched on, the mean SRTn values of the U-STARR and the Plomp test were 10.0 dB (SD 4.7) and 14.0 dB (SD 6.3), respectively (cf. Table 3). The difference was statistically significant ($p < 0.01$). Wearing a contralateral hearing aid did not have an effect on the Plomp or U-STARR test results ($p > 0.05$). When we tested with only the hearing aid switched on, none of the 12 patients were

able to repeat the (key words of the) sentences correctly in silence, let alone in noise. For that reason, an SRTn could not be measured, and a floor effect appeared. For this reason, we did not report the results for listening with a hearing aid only in table 3. The normal-hearing subjects performed significantly better on the Plomp test and the U-STARR than the CI patients ($p < 0.01$) (cf. Table 3).

Table 3 | Outcomes

A. Speech in noise tests

	Plomp (SNR in dB)	U-STARR (SNR in dB)	p-value	SISSS Best performing situation (SNR in dB)	SISSS Worst performing situation (SNR in dB)	p-value
Normal hearing group n=29	-3.7±1.5	-5.6±1.2	0.000	-16.3±1.8	-14.3±1.8	0.000
CI n=18	15.1±7.0	9.9±4.2	0.000	3.7±4.5	18.7±10.4	0.000
CI+HA n=12	14.0±6.3	10.0±4.7	0.003	4.2±3.9	17.3±7.2	0.000

SNR = signal-to-noise ratio, U-STARR = Utrecht Sentence Test at Randomized Roving Levels, SISSS = Sentences in spatially separated sources, CI = Cochlear implant, HA = Hearing aid

B. Localization tests

	60° (% correct)	Chance (%)	p-value	30° (% correct)	Chance (%)	p-value	15° (% correct)	Chance (%)	p-value
Normal hearing group n=29	100±0.0	33.33	0.000	100±0.0	20.00	0.000	99.5±0.0	20.00	0.000
CI n=18	40.4±8.1	33.33	0.005	23.3±8.6	20.00	NS	18.7±7.6	20.00	NS
CI+HA n=12	44.7±14.0	33.33	0.028	26.4±11.9	20.00	NS	24.4±10.8	20.00	NS

NS = not significant

Repeated Measures

Twelve subjects underwent the Plomp test and the U-STARR twice on separate days. Although different sentences were presented to them on these occasions, a slight

learning effect did occur in both the U-STARR and the Plomp test (cf. Table 4).

Table 4 | Repeated measures on the Plomp test and U-STARR, normal-hearing persons

	Test moment 1 Mean ± SD	Test moment 2 Mean ± SD	p-value
Plomp test (SNR in dB) n=12	-4.1 (1.1)	-5.1 (0.8)	0.028
U-STARR (SNR in dB) n=12	-5.5 (1.0)	-6.5 (0.9)	0.013

SD = standard deviation, SNR = signal-to-noise ratio , U-STARR = Utrecht Sentence Test at Randomized Roving Levels

Speech Intelligibility in Noise with Spatially Separated Sources

Seven normal-hearing subjects performed slightly better when sound came from the left and noise from the right (S –60 N +60). Two subjects performed equally well on both tests, and 20 performed slightly better when sound came from the right and noise from the left (S +60 N –60). The mean SRTn for the best performance condition (S –60 N +60 or S –60 N +60) was –16.3 dB (SD 1.8), and for the worst performance condition it was –14.3 dB (SD 1.8). There was a statistically significant difference in performance between the subjects' best and worst listening conditions ($p < 0.01$). Again, the variance in the normal-hearing group was small. For the CI group, when they were wearing only the CI and speech was presented to that side, a mean SRTn of 3.7 dB (SD 4.5) was found. When speech was presented to the contralateral side, a mean SRTn of 18.7 dB (SD 10.4) was found. The results for the best performance condition were clearly better than for the worst performance condition in CI patients ($p < 0.01$) (cf. Table 3). In the subgroup of 12 contralateral hearing aid users, a mean SRTn of 4.2 dB (SD 3.9) was found when both devices were worn and sound was presented to the CI side. A mean SRTn of 17.3 dB (SD 7.2) was found when sound was presented to the hearing aid side (cf. Table 3).

Wearing a contralateral hearing aid did not have any effect on the SISSS test results ($p > 0.05$). Normal-hearing persons performed significantly better on the SISSS test than CI users, irrespective of whether the cochlear implantees used a contralateral hearing aid ($p < 0.01$).

DISCUSSION

In a time in which cochlear implantation techniques keep improving and possibilities for sound processing strategies are growing, there is a need for sophisticated hearing tests that are representative of everyday listening situations. The AB-York crescent of sound provides a battery of hearing-in-noise and localization tests that mimic these everyday situations. We translated the English STARR into Dutch (the U-STARR) for our population. In the present study, the U-STARR has been validated and compared to the conventional Plomp test.

Speech in Noise from Straight Ahead in Normal-Hearing Persons

We have shown that in normal-hearing adults, the U-STARR is adequate and reliable compared to the conventional Plomp test. First, these individuals performed better on the U-STARR because it allowed them to make small mistakes. Nevertheless, subjects who performed well on the Plomp test performed well on the U-STARR and vice versa. Second, the variance in U-STARR results was low; in fact, it was even lower than in the Plomp test results. Third, when repeatedly tested on different occasions, subjects showed similar results. There was a small learning effect, which was equal in the U-STARR and the Plomp test. A similar small learning effect was described for the English STARR and the original Plomp test [4,8]. Fourth, the Dutch test results were almost identical to the English test results. Boyle et al. applied the STARR to 25 normal-hearing persons and found a mean SRT of –5.9 dB (SD 1.3) [8]. This is similar to the SRT of –5.7 dB (SD 1.3) we found with the Dutch version of this test [6].

Speech in Noise from Straight Ahead in CI Patients

This study also demonstrated that the U-STARR is suitable for measuring speech-in-noise performance in cochlear implantees. Hearing in noise is energy consuming for patients. If they have been deaf for a prolonged period of time, they may also lose the capability to articulate well. Both could result in a poorer Plomp test score. By scoring key words per sentence instead of full sentences, as was customary in the Plomp test, the test has become less demanding. It reduces the number of poor results, caused by small mistakes that have little influence on actually understanding a sentence correctly. The CI patients included in this study had all been able to hear in the past. For this reason, we were able to get a result for the Plomp test for all patients when they were

wearing their CI, without reaching a floor effect. However, 4 patients had a result of >20 dB SNR, which means that the sentences were presented in almost negligible noise [8]. On the U-STARR, only 1 patient had a result of little over 20 dB SNR. Because the U-STARR is more refined than the Plomp test and the variance within a group of CI patients is lower, it seems better suited for studies that investigate subtle differences (for instance, to compare effects of unilateral to bilateral cochlear implantation). Boyle et al. applied the STARR to 25 CI users [8]. Although the group was comparable to ours in terms of age, it is not clear whether the subjects had been able to hear in the past. This is very important, since prelingually deafened patients are much more likely to reach a floor effect, which significantly lowers a group outcome. The authors described that 3 patients performed so poorly that an SRTn could not be measured, and they were left out of the study. Another 12 patients reached an SRTn of >20 dB. The group mean of all 22 patients was therefore high: 28 dB (SD 20). The mean of the 10 best-performing patients, who all had SRTn results <20 dB, was 9.4 dB (SD 3). These latter results are comparable to the results for our CI patients (mean 9.9 dB, SD 4.2).

Spatial Listening in Normal-Hearing Persons

In SISSS testing, 20 out of the 29 normal-hearing subjects performed better when speech was presented to the right ear and noise to the left. Twenty-four of these persons were right-handed. This is in line with the idea that signals presented to the right ear have privileged access to language centers in the dominant left hemisphere in right-handed and most left-handed people when competing sounds are presented to both ears [10,11]. Five persons were left-handed, 2 of whom performed better with sound from the right and noise from the left. Two performed better with sound from the left and noise from the right, and 1 performed equally well in both situations.

Spatial Listening in CI Patients

With the AB-York crescent of sound, we were able to show that spatial listening was impossible for CI patients with only one implanted ear. The CI patients in our study performed similar to chance levels on the localization tests. This is comparable to the findings of Dunn et al., who performed an 8-loudspeaker sound localization test in unilaterally implanted, postlingually deafened adults [12,13]. Furthermore, it was very difficult to understand speech in noise when speech was presented to the non-implanted ear and background noise to the implanted ear in the SISSS test. Finally,

we aimed to test all CI users in three listening conditions, but we noticed that several patients did not wear a hearing aid on the contralateral ear out of their own choice because they did not experience any benefits from them. The subjects who did use a hearing aid on the contralateral side did not show any benefits from them in the speech-in-noise or localization tests.

CONCLUSION

We were able to adequately test speech-in-noise and spatial hearing capabilities in normal-hearing subjects and CI patients with the Dutch version of the AB-York crescent of sound. We validated the U-STARR by measuring a group of normal-hearing listeners and tested its reliability. We also demonstrated that the U-STARR is suitable for measuring speech in noise in severely hearing-impaired subjects and cochlear implantees. It mimics everyday listening situations better than the Plomp test by allowing subjects to use the context of words that are presented in sentences. For the hearing impaired, it is easier to undergo the U-STARR than the Plomp test, since, in the former, they are allowed to make small mistakes and the floor effect is not reached as fast as in the latter. The AB-York crescent of sound is now used in the UK and the Netherlands. Although the English test material was replaced by Dutch sentences, the test results in both languages were similar. The test material could also be used in other countries if it were replaced by sentences in different languages. This would make it possible to compare results between studies more easily in the future.

REFERENCES

1. Crathorne L, Bond M, Cooper C, Elston J, Weiner G, Taylor R, Stein K: A systematic review of the effectiveness and cost-effectiveness of bilateral multichannel cochlear implants in adults with severe-to-profound hearing loss. *Clin Otolaryngol* 2012; 37: 342–354.

2. Gaylor JM, Raman G, Chung M, Lee J, Rao M, Lau J, Poe DS: Cochlear implantation in adults, a systematic review and meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2013; 139: 265–272.

3. Van Schoonhoven J, Sparreboom M, van Zanten GA, Scholten RJPM, Mylanus EAM, Dreschler WA, Grolman W, Maat B: The effectiveness of bilateral cochlear implants for severe-to-profound deafness in adults: a systematic review. *Otol Neurotol* 2013; 34: 190–198.

4. Plomp R, Mimpen AM: Improving the reliability of testing the speech reception threshold for sentences. *Audiology* 1979; 18: 43–52.

5. Van Wieringen A, Wouters J: LIST and LINT: sentences and numbers for quantifying speech understanding in severely impaired listeners for Flanders and the Netherlands. *Int J Audiol* 2008; 47: 348–355.

6. Joffo L, Boyle P; Star 2 Validation Working Group: Cochlear implant users' everyday-life performance assessed in clinical practice. *Cochlear Implants Int* 2010; 11(suppl 2):52–56.

7. Kitterick PT, Lovett RES, Goman AM, Summerfield AQ: The AB-York crescent of sound: an apparatus for assessing spatial-listening skills in children and adults. *Cochlear Implants Int* 2011; 12: 164–169.

8. Boyle PJ, Nunn TB, O'Connor AF, Moore BC: STARR: a speech test for evaluation of the effectiveness of auditory prostheses under realistic conditions. *Ear Hear* 2013; 34: 203–212.

9. Versfeld NJ, Daalder L, Festen JM, Houtgast T: Method for the selection of sentence materials for efficient measurement of the speech reception threshold. *J Acoust Soc Am* 2000; 107: 1671–1684.

10. Studdert-Kennedy M, Shankweiler D: Hemispheric specialization for language processes. *Science* 1981; 211: 960–961.

11. Van der Haegen L, Westerhausen R, Hugdahl K, Brysbaert M: Speech dominance is a better predictor of functional brain asymmetry than handedness: a combined fMRI word generation and behavioral dichotic listening study. *Neuropsychologia* 2013; 51: 91–97.

12. Dunn CC, Tyler RS, Oakley S, Gantz BJ, Noble W: Comparison of speech recognition and localization performance in bilateral and unilateral cochlear implant users matched on duration of deafness and age at implantation. *Ear Hear* 2008; 29: 352–359.

13. Dunn CC, Tyler RS, Witt S, Ji H, Gantz BJ: Sequential bilateral cochlear implantation: speech perception and localization pre- and post-second cochlear implantation. *Am J Audiol* 2012; 21: 181–189.

CHAPTER 03

A randomized controlled trial showing a higher benefit of bilateral over unilateral cochlear implantation in adults

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ABSTRACT

Importance

Bilateral cochlear implantation (BiCI) is usually not reimbursed, because of a lack in well-designed studies demonstrating the benefits of a second cochlear implant.

Objectives

To determine what the benefits are of simultaneous BiCI compared to unilateral cochlear implantation (UCI), in postlingually deafened adults.

Design

We performed a multicenter randomized controlled trial between 2010 and 2012.

Setting

The study took place in five Dutch tertiary referral centers: the University Medical Centers of Utrecht, Maastricht, Groningen, Leiden and Nijmegen.

Participants

40 patients eligible for CI met the study criteria. The main inclusion criteria were postlingual onset of hearing loss, age between 18-70 years, duration of hearing loss of less than 20 years and a marginal hearing aid benefit. Two participants withdrew from the study before implantation. Nineteen participants were assigned to UCI and 19 to BiCI. No one was lost to follow-up.

Interventions

The BiCI group received 2 cochlear implants during one surgery. The UCI group received one cochlear implant. We used Advanced Bionics HiRes 90K® cochlear implants.

Main Outcomes and Measures

The primary outcome was the U-STARR (speech in noise, both presented from straight ahead). Secondary outcomes were CVC words in silence, SISSS (speech in noise from different directions), sound localization and quality of hearing questionnaires. Before we had collected any data, our hypothesis was the BiCI group would perform better

on the objective and subjective tests that concerned speech intelligibility in noise and spatial hearing.

Results

The groups were equal at baseline. At 1–year follow-up, there were no significant differences between groups on the U-STARR (median speech reception threshold in noise 9.1dB in the UCI group and 8.2dB in the BiCI group ($p>0.05$)) or CVC test. The BiCI group performed significantly better than the UCI group when noise came from different directions. They were also able to localize sounds. These results were consistent with the patients' self-reported hearing capabilities.

Conclusion

This is the first randomized controlled trial that demonstrates that there is a significant benefit of simultaneous bilateral CI over unilateral CI in daily listening situations, for postlingually deafened adults.

Trial Registration

Dutch Trial Register NTR1722.

INTRODUCTION

Worldwide, over 550 million people suffer from disabling hearing loss (pure-tone average (PTA) at 500, 1000 and 2000Hz ≥35dB HL in the better ear). Over 60 million suffer from severe hearing loss or worse (PTA≥65dB HL) [1]. For the latter group, a cochlear implant may be provided. Cochlear implantation (CI) has proven to be very successful, especially for patients who have well-developed central auditory pathways, i.e. in those who received an implant at an early age or who lost their hearing later in life after auditory cortex development [2]. In the Netherlands, CI is considered a treatment option if hearing aids (HAs) do not provide sufficient benefit. This means that the aided speech perception threshold in quiet; the phoneme score, measured with consonant-vowel-consonant (CVC) words, is 50% or less at 65dB SPL. Since 2012, bilateral implantation is standard care for children until the age of 5 years in the Netherlands. Adults only receive reimbursement for a second implant when deafness is caused by meningitis, which may lead to ossification of the cochlea. There is an on-going discussion in the Netherlands on whether or not bilateral CI should be standard care for adults, as it is in Germany and Scandinavia [3]. Binaural hearing enables one to differentiate sounds of interest from background noise and locate where sounds come from, by using different effects of binaural hearing: head shadow, squelch and summation [4-7]. Several reviewers have analyzed the benefits of BiCI compared to UCI. BiCI seems beneficial for speech perception in noise, localization of sounds and improvement of quality of hearing and quality of life, however, reviewers concluded that the majority of studies have a low level of evidence [8-10].For this reason, Dutch insurance companies have decided that reimbursement of a second cochlear implant in adults cannot be justified.

In this paper, we present the results of a multicenter, randomized controlled trial (RCT) on the benefits of simultaneous BiCI compared to UCI in adults with severe bilateral postlingual hearing loss. We present: 1) objective hearing test results for both hearing in noise and in quiet, which also includes sound localization capabilities, and 2) patients' self-reported quality of hearing results.

METHODS

Trial design and participants

In the Netherlands, CI is performed in 8 tertiary referral centers, 5 of which participated in this RCT; the University Medical Centers (UMCs) of Utrecht, Maastricht, Nijmegen, Leiden, and Groningen. The study criteria were verified for each patient eligible for CI, in the multidisciplinary CI teams, between January 2010 and September 2012 (cf. figure 1). The inclusion criteria were: 1. Age between 18 and 70 years, 2. Postlingual onset of hearing loss: participants attended mainstream education, 3. Duration of severe-to-profound hearing loss of less than 20 years in each ear and a difference in duration of hearing loss between the two ears of less than 10years, 4. Marginal hearing aid benefit, defined as an aided phoneme score < 50% at 65 dB SPL, 5. Dutch as native language, 6. Willingness and ability to participate in all scheduled procedures outlined in the protocol, 7. General health allowing general anesthesia for the duration of potential simultaneous BiCI, 8. Dutch health insurance coverage. 9. Agreement to be implanted with Advanced Bionics implants. Exclusion criteria were: 1. Previous cochlear implantation. 2. Disability that could interfere with the completion of the tests, 3. Abnormal cochlear anatomy in one or both ears, 4. Chronic ear infection in one or both ears. The criteria were double-checked by the main investigators in Utrecht before a patient received written information from his or her otolaryngologist and was asked to participate in the study. Baseline hearing tests were performed as part of the standard CI work-up and were equal in all centers. They encompassed standard pure tone audiometry and speech intelligibility in quiet, with and without hearing aids, using standard CVC words. After receiving informed consent, self-reported questionnaires on hearing were filled out at the patients' own hospitals, before participants were randomly allocated to either one of two treatment groups. This order was chosen because the knowledge of receiving one or two implants could influence the participant's answers and bias the results.

Randomization and masking

The participants were assigned to either 1) UCI or 2) simultaneous BiCI. The randomization program was designed by an independent data manager and could not be influenced by any of the researchers. We used a 'block randomization per center strategy' to obtain an equal distribution between UCI and BiCI in all centers. Blinding

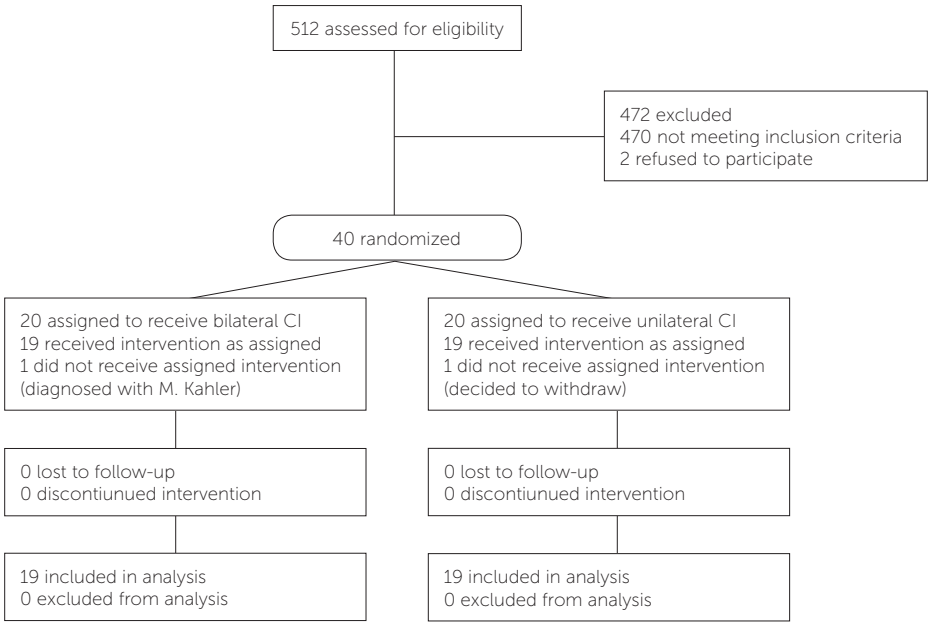
was not possible due to the nature of the study; one could see on the outside if a patient had one or two implants.

This study was approved by the Human Ethics Committees of all participating centers (NL24660.018.08) and was conducted according to the principles expressed in the Declaration of Helsinki.

Loss to follow-up

One participant, who was assigned to BiCI, was excluded when diagnosed with Kahler's disease only a few weeks later (Kahler's disease or multiple myeloma is a cancer in which antibody-producing plasma cells grow in an uncontrolled and invasive (malignant) manner). Another participant, who was assigned to UCI, decided to withdraw when his surgery was postponed due to a temporary recall of Advanced Bionics implants. These participants were replaced by new participants. All other patients completed the test sessions for the 1-year follow-up period (cf. figure 1).

Figure 1 | Flowchart of enrollment



This flowchart shows the number of patients eligible for cochlear implantation (CI), in whom the study criteria were assessed. The participants were randomly allocated to unilateral CI (UCI) or bilateral CI (BiCI). None were lost to follow-up.

Study procedures

All participants received Advanced Bionics HiRes90K® cochlear implants to ensure that they had access to the same technology. In the UCI group, patients chose the ear of implantation, which was usually the ear with the worst hearing. They were allowed to discuss their decision with members of the CI team, but made the choice them selves. Since the objective of the study was to compare BiCI with the next best alternative, the use of a contralateral hearing aid was encouraged in the UCI group. The surgery and rehabilitation took place in the patients' own hospital and rehabilitation started about six weeks after surgery. The implant processing strategy was defined in a protocol for all centers. All patients were fitted with Harmony processors except for two (one in each group) who used Neptune processors (that have an identical processing strategy, but a body worn microphone). Four weeks before testing, they switched to Harmony processors to allow time for acclimatization. All tests were performed wearing Harmony processors.

Test procedures at 1-year follow-up

One year after surgery all participants were asked to complete the quality of hearing questionnaires for the second time. Further spatial hearing tests were performed at the UMC Utrecht by 4 well-trained researchers who strictly followed the same protocol. All gathered data were double-checked by an independent person who did not have any other connections to the otorhinolaryngology department.

The Dutch AB-York crescent of sound

Speech intelligibility in noise and localization capabilities were tested with the Dutch AB-York crescent of sound [11,12]. The test battery included: 1. The U-STARR (Utrecht Sentence Test with Adaptive Randomized Roving levels), 2. A speech-intelligibility test with spatially separated sources (SISSS) and 3. A sound localization test. The AB-York crescent of sound contains 9 audio-visual stands, 7 positioned at 30° intervals and 2 at 15° intervals on either side of 0° (cf. Figure 2). In the U-STARR, Dutch "VU '98 sentences" were presented at 65, 70 or 75 dB SPL (randomly selected) in speech noise, both coming from straight ahead. The number of key words correctly repeated per sentence was scored. Sentences were presented with an initial signal-to-noise ratio (SNR) of +20dB (sentence 20dB louder than noise). If a sentence was scored as correct, the SNR for the next sentence was decreased by increasing the noise level.

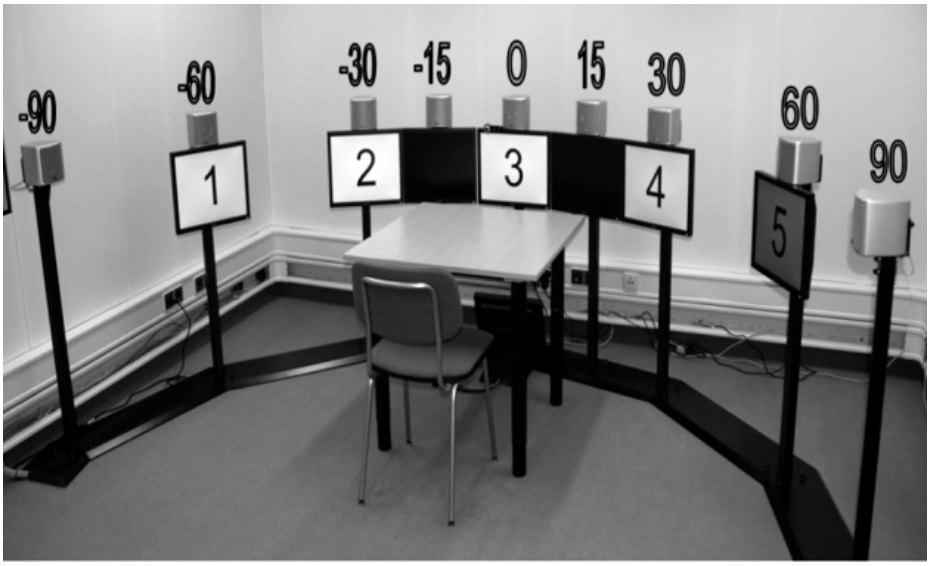
If a sentence was scored as incorrect, the SNR was increased. The SNR was changed with consecutive steps of 10, 5 and 2.5dB. The SNR average of the last ten sentences was calculated, which resulted in the speech reception threshold in noise (SRTn). For the SISSS, the same procedure was used as for the U-STARR. The only difference was that the sentences were presented from 60° to the left (-60° azimuth) or to the right (+60° azimuth) of the patient. For the sound localization test, numbers were shown on screens, representing the loudspeakers above them. A phrase was presented from one of the loudspeakers (randomly at 60, 65, or 70 dB SPL), 30 times in total. The results were percentage correct responses with 60, 30 and 15° angle between speakers. All tests were performed: first, monaurally, with either one of the cochlear implants or the HA switched on, then bilaterally, using both cochlear implants, or bimodally, with both cochlear implant and HA switched on. Participants were instructed to face the loudspeaker positioned in front of them and not to turn their head during the tests.

In order to compare BiCI to the next best option, we defined a "patient's preferred situation" for each patient in the UCI group. This was the daily hearing situation; either wearing the cochlear implant only or a cochlear implant and HA. Results from the BiCI group were compared to results of the "patient's preferred situations" from the UCI group.

When speech and noise come from different directions, one is best able to understand the speech when it is presented to the best hearing ear, and noise to the worst hearing ear. In the UCI group, this situation occurs when speech is presented to the CI side and noise to the contralateral side. Bilaterally implanted subjects generally also have one side with which they hear better than with the other.

Per participant, we defined this "best hearing situation" and the "worst hearing situation". The latter occurs when speech is presented to the worst hearing side and noise to the best hearing side.

Figure 2 | AB-York crescent of sound, test setup



This setup was used to conduct the Utrecht Sentence Test with Adaptive Randomized Roving levels (U-STARR), speech intelligibility test with spatially separated sources (SISSS) and localization tests.

OUTCOMES

The primary outcome was the U-STARR. Secondary outcomes were the SISSS, CVC words in quiet, sound localization and self-reported benefits in everyday listening situations assessed with the Speech, Spatial and Qualities Hearing Scale (SSQ) [13], Time trade-off (TTO) [14], Visual Analogue Scale (VAS) for hearing (0-100 scale) and Nijmegen Cochlear Implant Questionnaire (NCIQ) [15].

On the TTO, participants were asked how many life years they were willing to give up to live the rest of their lives with perfect hearing. TTO (%) = ((Life expectancy - amount of years to give up for perfect hearing) / Life expectancy) X100 [14]. This question needs a good instruction, therefore we decided not to let patients answer it in their own hospital preoperatively, but we asked them personally at the 1-year follow-up test moment at the UMC Utrecht.

Sample size calculation

To detect a clinically relevant difference of 3dB in signal-to-noise ratio (SNR) between groups on the hearing-in-noise test and a standard deviation of 3dB, with an alpha of

0.05 and a power of 80%, we calculated 14 subjects per group were needed. In order to compensate for any data lost to follow up, five additional subjects were included in each group. 3dB is magnitude of the summation effect that is typically observed.

Statistical analysis

To compare baseline characteristics and preoperative test results, we used the student's t-test for numeric, normally distributed data and the chi square test for ordinal data. None of the postoperative test results were normally distributed. We therefore present median outcomes and ranges. We used the Mann-Whitney U-tests for all hearing test results, the TTO, VAS and SSQ, for comparing unilateral with bilateral group data. For the NCIQ, we used the chi square test. In order to compare preoperative with postoperative findings, we used the Wilcoxon signed-rank test. To analyze if residual hearing had an effect on the outcomes, we calculated Spearman's rho correlation coefficients between the maximum CVC score (with or without hearing aid) and the U-STARR, SISSS and localization test results. In order to make it easier to compare our findings with literature, in which means and standard deviations are usually presented, we added means and standard deviations to table 2.

RESULTS

Patient characteristics and objective results

The baseline characteristics of the 38 included patients are summarized in table 1. Fifteen patients in the BiCI group used hearing aids before implantation, compared to 19 in the UCI group. Otherwise, there were no significant differences between the groups' baseline characteristics.

One year after implantation, hearing had clearly improved in both groups compared to the preoperative situation (cf. Table 2). Although there were no significant differences between groups on the U-STARR and CVC test, clear differences appeared when sounds came from different directions. When speech was presented to the non-implanted ear and noise to the implanted ear ("worst hearing situation"), the unilateral implantees performed significantly worse than the bilateral implantees in their "worst hearing situations" on the SISSS. Bilaterally implanted subjects showed significantly better results on all localization tests (cf. Table 2).

Residual hearing

In the UCI group, 7 out of 19 patients did not use a contralateral HA at 1-year follow-up, because they did not experience any benefits from it (cf. Table 2). The objective test outcomes did not correlate significantly with the maximum CVC scores with (n=12) or without (n=7) wearing HAs ($p>0.05$), which means that residual hearing did not influence the results.

Subjective results

Preoperatively, there were no differences between the UCI and BiCI group on the quality of hearing questionnaire results (SSQ, VAS on hearing and NCIQ) (cf. figure 3). One year postoperatively, all participants reported significant improvement on all questionnaires. At 1-year follow-up, the BiCI group showed significantly better results on the three chapters of the SSQ, VAS on hearing and TTO, than the UCI group. On the NCIQ, the BiCI group reported better hearing capabilities than the UCI group, but not significantly so (cf. Figure 3).

Table 1 | Patient characteristics

	Unilateral CI	Bilateral CI	p-value
Male:Female	11:08	08:11	0.33
Age at inclusion (yrs)	52.5 (12.5) [26-67]	47.7 (15.9) [18-70]	0.31
Age start severe hearing loss AD (yrs)	30.8 (20.1) [3-55]	30.5 (17.2) [3-63]	0.95
Age start severe hearing loss AS (yrs)	30.6 (19.8) [3-55]	30.0 (17.5) [3-63]	0.92
PTA AD (dB)	106.3 (12) [78-125]	106.1 (16) [80-130]	0.65
500Hz	84 (17.2) [35-115]	93 (21.3) [65-130]	0.15
1000Hz	97 (12.0) [70-115]	101 (17.0) [80-130]	0.44
2000Hz	104 (14.9) [70-130]	108 (17.7) [80-130]	0.46
4000Hz	118 (13.6) [90-130]	109 (18.5) [70-130]	0.12
PTA AS (dB)	107.5 (13) [83-127]	108.3 (18) [77-130]	0.67
500Hz	86 (20.6) [20-115]	93 (20.1) [65-130]	0.33
1000Hz	99 (15.1) [75-130]	103 (17.2) [80-130]	0.46
2000Hz	107 (14.1) [80-130]	111 (19.9) [75-130]	0.51
4000Hz	117 (14.3) [85-130]	111 (22.6) [65-130]	0.37
Max. phoneme score with hearing aids (%)	46.2 (20.4) [0-80]	42.1 (27.6) [0-90]	0.60
Treatment Hospital			0.89
Utrecht	11	8	
Maastricht	4	5	
Nijmegen	2	3	
Leiden	1	2	
Groningen	1	1	
Hearing aid use before CI			0.04*
Yes	19	15	
No	0	4	
Cause of deafness			0.25
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	

Mean (standard deviation) [range], UCI = unilateral cochlear implantation, BiCI = bilateral cochlear implantation, AD = right ear, AS = left ear, PTA (pure tone audiogram) - average at 0.5, 1 and 2 kHz. * = significant, $p<0.05$. The items in bold are made up of the values associated with the sub-items below them. A significance value is given alongside the item in bold.

Table 2 | Objective outcomes one year postoperative

		Unilateral group	Bilateral group	
		Patient preferred situation (+/- HA)	Patient preferred situation (+/- HA)	p-value
		n=19	n=19	
Residual hearing non-implanted ear				
HA-users (n=12)	mean±SD	22.7±22.7		
	median [range]	22.5 [0-65]		
Non-HA users (n=7)	mean±SD	8.3±21.9		
	median [range]	0 [0-58]		
Whole UCI group	mean±SD	17.4±23.0		
	median [range]	0 [0-65]		
Speech-in-noise and in silence				
Speech-in-noise both from straight ahead (SRTn in dB)	mean±SD	10.0±6.3	8.2±5.3	
	median [range]	9.1 [2.2-30]	8.2 [0.3-18.4]	0.39
Phoneme score in silence (CVC in %)	mean±SD	83.4±8.9	86.8±9.5	
	median [range]	85.0 [70-98]	88.0 [67-100]	0.21
Speech and noise from different directions				
SISSS Best performing situation (SRTn in dB)	mean±SD	5.9±7.3	4.1±5.9	
	median [range]	5.0 [-3.1-30.0]	4.1 [-4.7-14.1]	0.61
SISSS Worst performing situation (SRTn in dB)	mean±SD	15.8±6.3	7.1±7.5	
	median [range]	14.4 [8.1-30.0]	5.6 [-2.8-22.8]	<0.01*
Localization of sounds				
60° (% correct)	mean±SD	50.5±16.5	93.7±7.8	
	median [range]	50.0 [30.0-90.0]	96.7 [73.3-100.0]	<0.01*
30° (% correct)	mean±SD	30.9±10.2	71.8±14.0	
	median [range]	30.0 [16.7-50.0]	76.7 [43.3-96.7]	<0.01*
15° (%correct)	mean±SD	29.0±8.8	56.7±16.3	
	median [range]	30.0 [20.0-50.0]	53.3 [33.3-90.0]	<0.01*

UCI = unilateral cochlear implantation, BiCI = bilateral cochlear implantation, HA = hearing aid, SRTn = speech reception threshold in noise, CVC = consonant-vowel-consonant words, SISSS = speech in spatially separated sources, NS = not significant (p>0.05), * = significant (p<0.05).

Figure 3

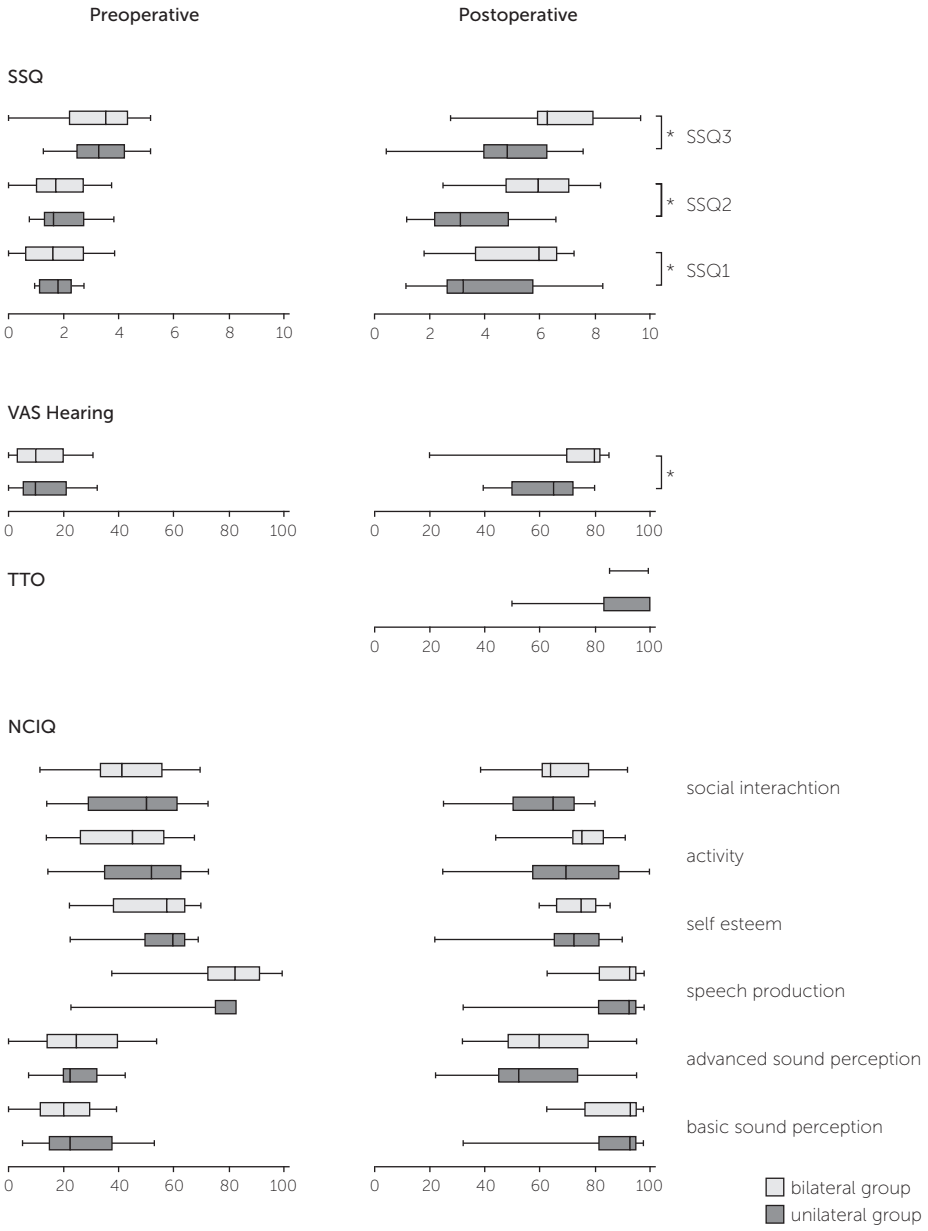


Figure 3 shows the preoperative and 1-year postoperative results on 3 quality of hearing questionnaires, in 19 unilaterally and 19 bilaterally implanted patients. SSQ = Speech, Spatial and Qualities Hearing Scale, SSQ 1 = Speech understanding in silence, in background noise, resonating environments and on the phone, SSQ 2 = spatial listening, SSQ 3 = Quality of hearing, VAS = Visual Analogue Scale, TTO = Time Trade Off, NCIQ = Nijmegen Cochlear Implant Questionnaire, Pre = Preoperative, Post = Postoperative, X-axis = scale points, * = Significant difference ($p<0.05$).

DISCUSSION

We present the results of the first RCT, investigating the benefits of simultaneous BiCI compared with UCI in postlingually deafened adults. In quiet, or when sound was presented to the patients implanted ear, unilaterally implanted patients performed equally well as bilaterally implanted patients. However, in everyday life, sounds come from different directions and there is usually background noise present. Our study shows that bilaterally implanted patients significantly benefit from their second implant in these situations.

Comparison with the literature

Most studies published on the potential benefits of BiCI versus UCI are non-randomized cohort studies, and often, bilateral implantees were asked to de-activate one implant to assess differences between unilateral and bilateral hearing. This is not representative for actual UCI as the patients were used to listening with two implants in daily life. Also, implantation would have caused insertion damage to the cochlea, deteriorating residual hearing [8]. As in our study, prior studies demonstrated that bilateral implantation did not improve speech-in-noise understanding when both were presented from straight ahead [16-18], although a summation effect has occasionally been found [19]. Dunn et al. (2010) assessed speech perception in noise, from separated sources, on 60 matched simultaneous bilateral and unilateral cochlear implantees [20]. As in our study, the former performed better than the latter. In our study, the patients in the BiCI group were able to localize sounds, which was difficult for the UCI group. Several other studies have demonstrated that bilateral implantation makes sound localization possible [18,21-25]. The quality of hearing questionnaire results confirmed the objective findings. The BiCI group evaluated their own performance in difficult listening situations, as represented in the SSQ, better than the UCI group. They also evaluated their overall hearing better on the VAS. As in our study, Summerfield et al. (2006) reported a significant positive effect of a second cochlear implant in 24 unilateral cochlear implant users on the SSQ [26]. Noble and colleagues (2008) compared 70 patients fit with one implant to 36 patients fit with bilateral implants (31 simultaneously and 5 sequentially) and also reported significantly better results in the BiCI group on the SSQ [23]. On the TTO, our two study groups showed comparable results, which were similar to the results of Kuthubutheen et al. [27]. On the NCIQ, Hinderink et al. (2000) reported comparable

findings of 47 postlingually deafened UCI patients [15]. There is no literature on NCIQ results in BiCI patients. Interestingly, there were no differences between the UCI and BiCI group on the NCIQ. All participants had developed speech before losing their hearing, which explains the lack of difference on this sub domain within and between groups. Apparently, a second implant did not have an additional value on changes in the subjects' self-esteem, activity levels or social interactions. The NCIQ contains questions on hearing in easy and difficult situations, but does not focus on spatial hearing like the SSQ. This might explain why the results of the BiCI group are better, but not significantly so.

Strengths and weaknesses

The major strength of our study was that allocation bias was minimized by using an RCT. Furthermore, the study group was homogeneous by setting strict in- and exclusion criteria, and none of the patients were lost to follow-up after they had been implanted. In the UCI group, the contralateral cochlea was untreated and most patients used a hearing aid in order to exploit that ear's even minimal function. We tested the participants after 1 year of implantation experience, which gave the brain time to adapt to this listening situation. A possible weakness of our study was that the patients were treated in 5 different centers and that the included numbers of patients per center varied. We attempted to minimize this potential bias by using a per center block randomization strategy. Furthermore, the researchers and caregivers were not blinded. However, we used a strict test protocol to minimize differences in testing between researchers.

CONCLUSION

This is the first report of an RCT showing the benefits of simultaneous BiCI over UCI in adults in various listening situations. Although a second cochlear implant did not have an additional value in easy listening conditions, bilaterally implanted subjects showed significantly better hearing results when sounds came from different directions, like in everyday noisy environments. This was demonstrated with objective hearing test results that were consistent with the participants' self-reported hearing capabilities.

REFERENCES

1. Stevens G, Flaxman S, Brunskill E, Mascarenhas M, Mathers CD, Finucane M. Global Burden of Disease Hearing Loss Expert Group. Global and regional hearing impairment prevalence: an analysis of 42 studies in 29 countries. *Eur J Pub Health* 2013;23(1):146-52.

2. Sharma A, Dorman MF, Spahr AJ. A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear Hear* 2002;23:532–9.

3. CI-ON (Cochleaire Implantatie Overleg Nederland) 19 december 2012. Richtlijn indicatie bilaterale cochleaire implantatie voor kinderen van 5 tot en met 18 jaar. In English: CI-ON (Dutch cochlear implantation group) 19 December 2012. Guideline indication bilateral cochlear implantation in children of 5-18 years of age.

4. Middlebrooks JC, Green DM. Sound localization by human listeners. *Ann Rev Psychol* 1991;42:135-59.

5. Bronkhorst AW, Plomp R. The effect of head-induced interaural time and level differences on speech intelligibility in noise. *J Acoust Soc Am* 1988;83:1508-16.

6. Dirks DD, Wilson RH. The effect of spatially separated sound sources on speech intelligibility. *J Speech Hear Res* 1969;12:5-38.

7. MacKeith NW, Coles RRA. Binaural advantages in hearing of speech. *J Laryngol Otol* 1971; 85:213-32.

8. Crathorne L, Bond M, Cooper C et al. A systematic review of the effectiveness and cost-effectiveness of bilateral multichannel cochlear implants in adults with severe-to-profound hearing loss. *Clin Otolaryngol* 2012;37:342–54.

9. Schoonhoven van J, Sparreboom M, Zanten van GA et al. The Effectiveness of Bilateral Cochlear Implants for Severe-to-Profound Deafness in Adults: A Systematic Review. *Otol Neurotol* 2013;34(2):190-8.

10. Gaylor JM, Raman G, Chung M et al. Cochlear Implantation in Adults, A Systematic Review and Meta-analysis. *JAMA Otolaryngol Head Neck Surg* 2013;139(3):265-72.

11. Kitterick PT, Lovett RES, Goman AM, Summerfield AQ. The AB-York crescent of sound: an apparatus for assessing spatial-listening skills in children and adults. *Cochlear Implants Int* 2011;12(3):164-9.

12. Smulders YE, Rinia AB, Pourier VEC et al. Validation of the U-STARR with the AB-York Crescent of Sound, a New Instrument to Evaluate Speech Intelligibility in Noise and Spatial Hearing Skills. *Audiol Neurotol Extra* 2015;5:1-10.

13. Gatehouse S, Noble W. The Speech, Spatial and Qualities of Hearing Scale (SSQ). *Int J Audiol* 2004;43:85–99.

14. Torrance GW. Measurement of health state utilities for economic appraisal, a review. *J Health Econ* 1986;5:1-30.

15. Hinderink JB, Krabbe PFM, Broek van den P. Development and application of a health-related qualityof-life instrument for adults with cochlear implants: The Nijmegen Cochlear Implant Questionnaire. *Otolaryngol Head Neck Surg* 2000;123:756-65.

16. Laszig R, Aschendorff A, O'Driscoll M, et al. Benefits of bilateral electrical stimulation with the nucleus cochlear implant in adults: 6-month postoperative results. *Otol Neurotol* 2004;25:958-68.

17. Litovsky R, Parkinson A, Arcaroli J, Sammeth C. Simultaneous bilateral cochlear implantation in adults: a multicenter clinical study. *Ear Hear* 2006;27:714-31.

18. Litovsky RY, Parkinson A, Arcaroli J. Spatial Hearing and Speech Intelligibility in Bilateral Cochlear Implant Users. *Ear Hear* 2009;30:419-31.

19. Buss E, Pillsbury HC, Buchman CA, et al. Multicenter U.S. bilateral MED-EL cochlear implantation study: speech perception over the first year of use. *Ear Hear* 2008;29(1):20-32.

20. Dunn CC, Noble W, Tyler RS, Kordus M, Gantz BJ, Ji H. Bilateral and Unilateral Cochlear Implant Users Compared on Speech Perception in Noise. *Ear Hear* 2010;31:296-8.

21. Dunn CC, Tyler RS, Oakley S, Gantz BJ, Noble W. Comparison of speech recognition and localization performance in bilateral and unilateral cochlear implant users matched on duration of deafness and age at implantation. *Ear Hear* 2008;29:352-9.

22. Neuman AC, Haravon A, Sislian N, Waltzman SB. Sound-direction identification with bilateral cochlear implants. *Ear Hear* 2007;28:73-82.

23. Noble W, Tyler R, Dunn C, Bhullar N. Unilateral and bilateral cochlear implants and the implant-plus-hearing-aid profile: comparing self-assessed and measured abilities. *Int J Audiol* 2008b;47:505-14.

24. Grantham DW, Ashmead DH, Ricketts TA, Labadie RF, Haynes DS. Horizontal-plane localization of noise and speech signals by postlingually deafened adults fitted with bilateral cochlear implants. *Ear Hear* 2007;28:524-41.

25. Noble W, Tyler RS, Dunn CC, Bhullar N. Younger- and Older-Age Adults With Unilateral and Bilateral Cochlear Implants: Speech and Spatial Hearing Self-Ratings and Performance. *Otol Neurotol* 2009;30:921-9.

26. Summerfield AQ, Barton GR, Terushkin V, et al. Self reported benefits from successive bilateral cochlear implantation in post-lingually deafened adults: Randomized controlled trial. Int J Audiol 2006;45:S99-107.

27. Kuthubutheen J, Mittmann N, Amoodi H, Qian W, Chen JM. The effect of different utility measures on the cost-effectiveness of bilateral cochlear implantation Laryngoscope 2014;00:000–000.

CHAPTER 04

Cost–utility of bilateral versus unilateral cochlear implantation in adults; a randomized controlled trial

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ABSTRACT

Objective

To study the cost-utility of simultaneous bilateral cochlear implantation (CI) versus unilateral CI.

Study Design

Randomized controlled trial (RCT).

Setting

Five tertiary referral centers.

Patients

38 postlingually deafened adults eligible for cochlear implantation.

Interventions

A cost–utility analysis was performed from a health insurance perspective.

Main Outcome Measures

Utility was assessed using the HUI3, TTO, VAS on hearing, VAS on general health and EQ-5D. We modeled the incremental cost per quality-adjusted life year (QALY) of unilateral versus bilateral CI over periods of 2, 5, 10, 25 years, and actual life-expectancy.

Results

Direct costs for unilateral and bilateral CI were €43,883 $\pm$ €11,513(SD) and €87,765 $\pm$ €23,027(SD) respectively. Annual costs from the second year onward were €3,435 $\pm$ €1,085(SD) and €6,871 $\pm$ €2,169(SD) respectively. A cost-utility analysis revealed that a second implant became cost-effective after a 5-10-year period, based on the HUI3, TTO and VAS on hearing.

Conclusion

This is the first study that describes a cost-utility analysis to compare unilateral with simultaneous bilateral CI in postlingually deafened adults, using a multicenter RCT. Compared to accepted societal willingness-to-pay thresholds, simultaneous bilateral CI is a cost-effective treatment for patients with a life expectancy of 5-10 years or longer.

INTRODUCTION

Cochlear implantation (CI) has proven to be a successful treatment for severe deafness. In several countries, like Germany and Scandinavia, health insurance companies reimburse bilateral CI for both adults and children. In the Netherlands, bilateral implantation is reimbursed for children (up until 19 years), but not for adult patients, since the effectiveness and cost-effectiveness of a second implant have not been adequately proven in this group of patients.

For healthcare policy makers, cost-utility (or cost-effectiveness) analyses are important tools for decision making. A cost-utility analysis depends on many different factors, both on the cost- and the utility-side of the equation. Costs can be estimated from the perspective of a society, patient, Ministry of Health, or health insurance company and encompass direct and indirect costs. Costs can be modeled over different periods of time, and for this, analysts usually apply sensitivity analyses and discounting methods [1].
The utility-side of the equation depends on the choice of quality of life (QoL) questionnaires being used and on how and by whom they are completed [2]. For the interpretation of cost-utility outcomes, it is important to be aware of the above-mentioned factors.

Furthermore, each country has its own generally accepted willingness-to-pay (WTP) threshold. In North America, this threshold is about $50,000/QALY (quality-adjusted life year) and in the UK, £20,000-£30,000. In the Netherlands, the WTP varies between €24,500 and €80,000, dependent on the seriousness of the disease [3-5].

In 2011, Lammers et al. systematically reviewed the literature on cost-utility of bilateral CI in adults and children [6]. The authors reported a large spread in gain of QALYs and incremental cost-utility ratios (ICURs). The latter varied between $30,973 and $132,160 per QALY. They concluded that the literature on cost-utility analyses of bilateral CI was sparse and ambiguous and stated that more empirical studies were needed [6].

In 2010, we started a multicenter randomized controlled trial (RCT) in order to systematically investigate the effectiveness and cost-utility of bilateral versus unilateral CI in postlingually deafened adults. In this article, we will present the results of a cost-

utility analysis, comparing unilateral CI with simultaneous bilateral CI in postlingually deafened adults.

MATERIALS AND METHODS

Trial design and participants

To evaluate the cost-utility of bilateral CI, we used the findings of a multicenter RCT that investigates both the effectiveness and cost-utility of unilateral versus simultaneous bilateral CI. A sample size calculation was performed, based on the primary outcome measure: speech understanding in noise. To detect a clinically relevant difference of 3dB in signal-to-noise ratio (SNR) between groups and a standard deviation of 3dB, with an alpha of 0.05 and a power of 80%, 14 subjects per group were needed. In order to compensate for any data lost to follow up, 5 additional subjects were included in each group.

Between January 2010 and September 2012, we included 38 adult patients, who met the following inclusion criteria: 1. Age between 18-70 years, 2. Postlingual onset of hearing loss (participants attended mainstream education), 3. At least severe sensory hearing loss in both ears (PTA≥70dB HL), 4. Comparable duration of hearing loss in both ears (difference between the ears ≤10years), 5. Ability to hear (with hearing aids) until at least 10 years ago, 6. Marginal hearing aid benefit (aided phoneme score ≤50% at 65dB SPL), 7. Dutch language proficiency, 8. General health allowing anesthesia for the duration of potential bilateral CI. 9. Dutch health insurance, 10. Agreement to be implanted with Advanced Bionics cochlear implants. Patients were excluded: 1. When they had been implanted with cochlear implants before, 2. When the anatomy of their cochleae was abnormal, or 3. If they experienced chronic ear infections.

This trial is a collaboration between 5 tertiary referral centers in the Netherlands: the University Medical Centers of Utrecht (n=19), Maastricht (n=9), Leiden (n=3), Nijmegen (n=5) and Groningen (n=2).

Randomization and masking

Using a web-based randomization program, designed by an independent data manager (Julius Center, UMC Utrecht), the subjects were randomized into two groups. This

procedure could not be influenced by any of the parties involved in the study. By using a 'block randomization per center strategy, the distribution between the two groups should be equal in all centers. The participants were allocated to the unilateral group (n=19) or simultaneous bilateral group (n=19). Blinding was not possible due to the nature of the study; one could see on the outside if a patient had one or two implants. This study was approved by the Human Ethics Committees of all participating centers (NL24660.018.08) and was conducted according to the principles expressed in the Declaration of Helsinki.

Quality of life

Utility was measured using QoL and quality of hearing questionnaires. Before implantation and after a 1- and 2-year follow-up period, we asked the participants to complete the following questionnaires:

1. Health Utilities Index 3 (HUI3). This standardized self-reporting questionnaire measures eight elements of health status: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each dimension has up to six levels. From the answers, a multi-attribute health status can be calculated, which is a utility score between -0.36 and 1 [7].
2. Time trade-off (TTO). Participants were asked how many life years they were willing to give up to live the rest of their lives with perfect hearing. TTO = ((Life expectancy - amount of years to give up for perfect hearing) / Life expectancy). The outcome is a utility score between 0 and 1 [8]. This question needs good instruction, and we decided not to let patients answer it in their own hospital preoperatively, but asked them personally at the one- and two-year follow-up test moments at the UMC Utrecht.
3. EuroQol 5D. The EQ-5D is one of the most widely used instruments to measure health utility. It contains a visual analogue scale indicating general health state (scale 0-100) and questions on 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The result is a single index value for health status between -0.33 and 1 [9,10].
4. Visual Analogue Scale for hearing (VAS). Participants were asked to rate their overall hearing on a 0-1 scale.
5. Visual Analogue Scale for general QoL of life (VAS). Participants were asked to rate their general QoL on a 0-1 scale.

Cost analysis

The cost analysis was performed from a health insurance perspective. In the remainder of this paper, costs will be expressed in 2013 euros. (Exchange rate at 1 January 2013: €1 = $1.34 = £0.84). In the Netherlands, insurance companies negotiate with all hospitals on the price they are willing to pay for a full treatment of a certain disease or diagnosis. A treatment includes all outpatient visits, surgery, hospitalization, imaging, and etcetera. The prices of CI are not publically accessible for legal and competition considerations, nor are the costs per unit of health care. A reliable bottom-up approach for cost-estimation was therefore not well feasible and we chose to use a top-down approach, based on ad hoc visitor's prices or so called "passenger prices". These are the amounts non-insured patients are charged for CI and published on each hospital's website. We used the 2013 pricelists of all 5 hospitals and calculated mean passenger prices and standard deviations (cf. Table 2). For the cost estimation of bilateral CI in adults, we doubled the passenger prices of unilateral CI.

In order to get a more detailed impression of direct and indirect costs, we also analyzed the amounts of visits the participants paid to the hospital, and their travel expenses. Additionally, we included the duration of the operations, and the duration of the associated hospital admission periods (cf. Table 2).

Sensitivity analysis

Quality-adjusted life years (QALYs) were calculated by multiplying utility scores with periods of 2, 5, 10, 25 years and the actual life expectancy of patients. The life expectancy of a cochlear implant is generally accepted to be 25 years. Although QoL is not expected to change rapidly in the years after implantation, modeling utility for 25 years, based on the outcome of 2 executive questionnaires, seemed long. Calculating QALYs only for the two years of the duration of the study would not be representative, because the costs in the year of implantation are clearly much higher than in the years afterwards, and patients are likely to benefit from their second implant much longer. We decided to model QALYs for different periods of time. The actual survival rates of the participants were 32.1$\pm$12.7(SD) years in the unilateral group, and 37.4$\pm$15.6(SD) years in the bilateral group.

Statistical analysis

In order to compare mean amounts of visits paid to the hospital, duration of surgery,

duration of hospital admission and travel expenses between the unilateral and bilateral group, we used the student's *t*-test (cf. Table 2). None of the QoL questionnaire results were normally distributed. We thus calculated medians and used the Mann-Whitney U-test to compare unilateral and bilateral group results (cf. Table 3). In order to be able to compare our findings with literature, in which means are usually presented, we also described group means in Table 3.

Loss to follow-up

One person in the unilateral group decided to withdraw from the study for personal reasons, after she had completed her one-year follow-up period. The second-year outcomes for this person are missing. Furthermore, there were no missing data.

RESULTS

The study groups were equal at baseline (cf. Table 1). All participants were Dutch and Dutch was their native language.

Costs

Table 2 describes the costs of unilateral and bilateral CI per year. The three "passenger prices" applicable are: 1.Costs of the first year of CI, including preoperative assessments, surgery and revalidation (€43,883 ± €11,513(SD) and €87,765 ± €23,027(SD) for unilateral and bilateral implantation respectively), 2. Costs of a consecutive year, including cochlear implant maintenance, possible processor replacement and hospital visits (€3,435 ± €1,085(SD) and €6,871 ± €2,169(SD) respectively), 3. Costs of electronystagmography (ENG). Fifty percent of the patients included in this study underwent an ENG (€654 ± €212(SD) for both unilateral and bilateral implantation).

Table 2 also demonstrates that there were no differences in numbers of preoperative assessments or travel expenses between the unilateral and bilateral group. Although the duration of bilateral implantation surgery was longer than unilateral implantation (287 versus 177 minutes), the hospital admission period was equal in both groups. Interestingly, there were no group differences in the amounts of postoperative evaluation moments or travel expenses (cf. Table 2).

Table 1 | Patient characteristics

	Unilateral CI	Bilateral CI	p-value
Male:Female	11:8	8:11	NS
Age at inclusion (yrs)	52.5 (12.5) [26-67]	47.7 (15.9) [18-70]	NS
Age start severe hearing loss AD (yrs)	30.8 (20.1) [3-55]	30.5 (17.2) [3-63]	NS
Age start severe hearing loss AS (yrs)	30.6 (19.8) [3-55]	30.0 (17.5) [3-63]	NS
PTA AD (dB)	106 (12) [78-125]	106 (16) [80-130]	NS
PTA AS (dB)	108 (13) [83-127]	108 (18) [77-130]	NS
Max. phoneme score with hearing aids (CVC in %)	46.2 (20.4) [0-80]	42.1 (27.6) [0-90]	NS
Treatment Hospital			NS
Utrecht	11	8	
Maastricht	4	5	
Nijmegen	2	3	
Leiden	1	2	
Groningen	1	1	
Hearing aid use before CI			0.04
Yes	19	15	
No	0	4	
Cause of deafness			NS
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	

CI = cochlear implantation, AD = right ear, AS = left ear, PTA = pure tone audiometry, CVC = consonant-vowel-consonant. Mean (SD) [range] are displayed for Ages, PTA and phoneme score. All other numbers are absolute amounts of patients. NS = not significant (p>0.05).

Table 2 | Costs of unilateral and bilateral cochlear implantation per person per year

	Unilateral CI	Bilateral CI	p-value
Direct healthcare costs			
Cochlear Implantation	43,883 (11,513)	87,765 (23,027)	
Annual follow-up costs	3,435 (1,085)	6,871 (2,169)	
ENG	654 (212)	654 (212)	
Preoperative			
Otolaryngologist (# visits)	3.4 (1.0)	3.2 (1.0)	NS
Audiologist (# visits)	2.6 (1.9)	3.0 (2.0)	NS
Speech therapist (# visits)	1.2 (0.8)	0.9 (0.7)	NS
Social worker / psychologist (# visits)	1.5 (0.5)	1.4 (0.6)	NS
Audiometry (# visits)	2.8 (1.4)	2.6 (1.0)	NS
ENG (#)	0.4 (0.5)	0.5 (0.5)	NS
CT scan (#)	1.0 (0.4)	1.0 (1.1)	NS
MRI scan (#)	0.3 (0.5)	0.2 (0.4)	NS
Direct non-healthcare costs			
Travel expenses	70.57 (47.15)	77.10 (50.94)	NS
Admission			
Duration admission (days)	3.7 (1.0)	3.6 (0.7)	NS
Duration surgery (min)	177 (39.4)	286.5 (86.6)	0.00
First year after surgery			
Otolaryngologist (# visits)	2.5 (1.5)	2.3 (1.7)	NS
Audiologist (# visits)	8.6 (2.0)	10.2 (4.4)	NS
Speech therapist (# visits)	8.8 (4.4)	10.1 (4.9)	NS
Social worker / psychologist (# visits)	1.6 (1.6)	1.8 (2.3)	NS
Audiometry (# visits)	2.3 (1.6)	2.4 (2.4)	NS
Direct non-healthcare costs			
Travel expenses	168.62 (123.75)	197.70 (170.26)	NS
Second year after surgery			
Otolaryngologist (# visits)	0.7 (0.8)	0.7 (1.1)	NS
Audiologist (# visits)	1.6 (1.8)	2.9 (2.8)	NS
Speech therapist (# visits)	0.8 (0.6)	1.2 (0.5)	NS
Social worker / psychologist (# visits)	0.3 (0.6)	0.6 (0.8)	NS
Audiometry (# visits)	1.2 (0.9)	1.1 (1.6)	NS
Direct non-healthcare costs			
Travel expenses	56.08 (39.06)	56.43 (55.45)	NS

All costs are expressed in 2013 euros (mean (SD)). # Visits = number of visits (mean (SD)). CI = cochlear implantation, ENG = electronystagmography, NS = not significant (p>0.05).

Utility

Before CI, utility scores were equal in both groups on all questionnaires. One year after implantation, utility was higher in bilaterally implanted patients on the VAS on hearing. On the other questionnaires, (HUI3, EQ-5D, TTO and VAS on general health), there were no significant differences between groups (cf. Table 3).

Cost–utility

Cost–utility analyses were performed for periods of 2, 5, 10, 25 years, and for the actual life expectancy of participants. Over these periods, ICURs of bilateral versus unilateral implantation were calculated. ICUR = (costs of bilateral implantation - costs of unilateral implantation (in euros)) / (utility of bilateral implantation – utility of unilateral implantation (in QALYs)).

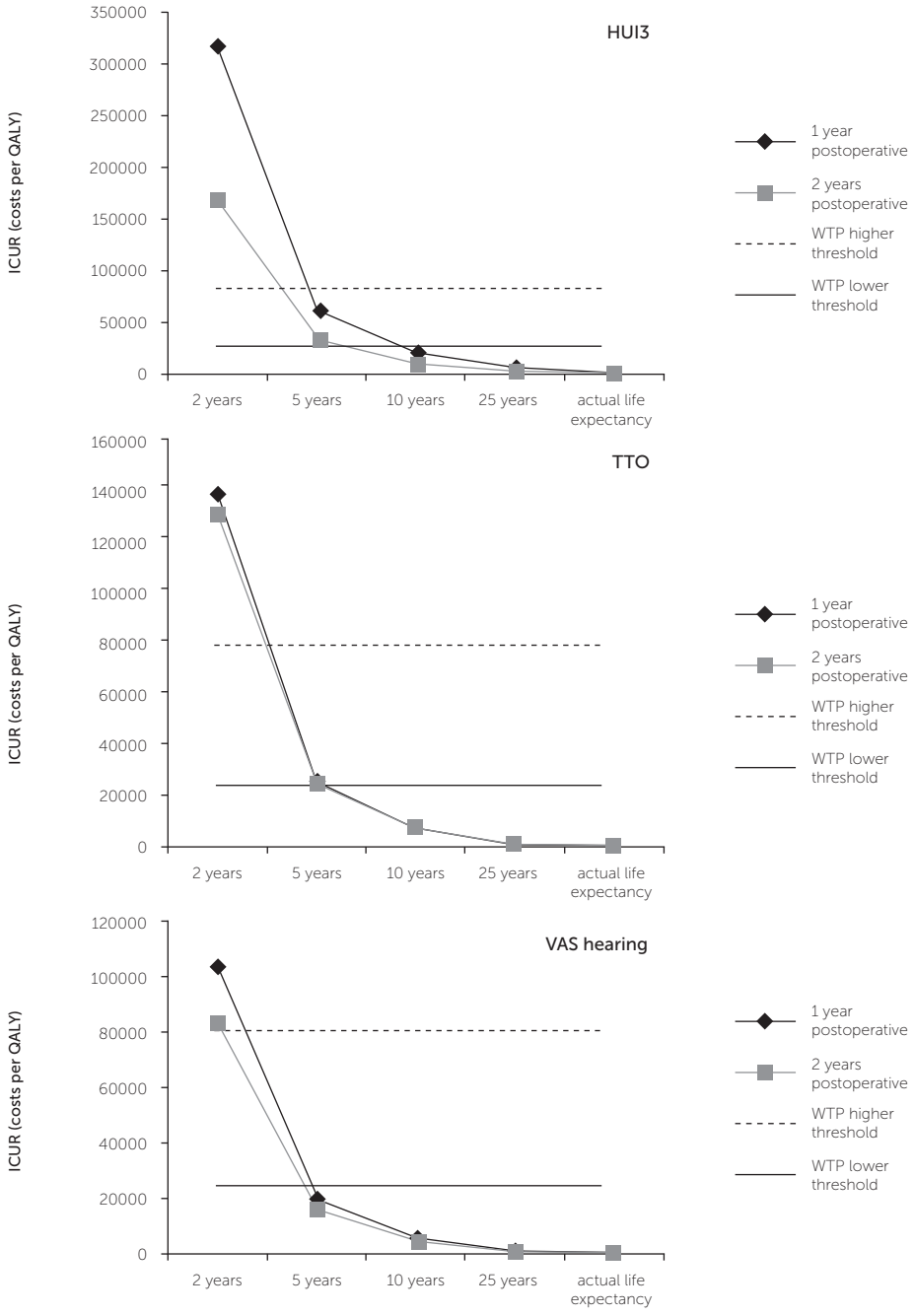
Figure 1 graphically shows the ICURs for different periods of time, based on the HUI3, TTO and VAS on hearing. The Dutch society's WTP is displayed in each graph (i.e. €24 500 - €80 000 per QALY), which shows that a second cochlear implant becomes cost-effective after 5 to 10 years of use. The differences between utility scores on the EQ-5D and VAS on general health were so small that they led to absurdly high ICURs. Based on these questionnaires, a second implant was not cost-effective.

Table 3 | Utility outcomes

			Unilateral CI	Bilateral CI	p-value unilateral vs bilateral CI
HUI3	Preoperative	Mean	0.58	0.56	
		Median	0.57	0.59	NS
	1 Year Postoperative	Mean	0.68	0.71	
		Median	0.78	0.78	NS
	2 Years Postoperative	Mean	0.68	0.72	
		Median	0.74	0.78	NS
EQ-5D, utility	Preoperative	Mean	0.95	0.93	
		Median	1.00	1.00	NS
	1 Year Postoperative	Mean	0.93	0.90	
		Median	1.00	1.00	NS
	2 Years Postoperative	Mean	0.94	0.92	
		Median	1.00	1.00	NS
EQ-5D, thermometer	Preoperative	Mean	84.16	81.42	
		Median	80.00	80.00	NS
	1 Year Postoperative	Mean	80.05	79.47	
		Median	80.00	75.00	NS
	2 Years Postoperative	Mean	82.61	77.32	
		Median	85.00	77.00	NS
TTO	Preoperative		NA	NA	
	1 Year Postoperative	Mean	0.91	0.99	
		Median	1.00	1.00	NS
	2 Years Postoperative	Mean	0.90	0.99	
		Median	1.00	1.00	NS
VAS, hearing	Preoperative	Mean	0.16	0.13	
		Median	0.10	0.10	NS
	1 Year Postoperative	Mean	0.63	0.74	
		Median	0.65	0.80	0.02
	2 Years Postoperative	Mean	0.57	0.72	
		Median	0.66	0.75	NS
VAS, health	Preoperative	Mean	0.66	0.72	
		Median	0.70	0.80	NS
	1 Year Postoperative	Mean	0.79	0.75	
		Median	0.80	0.80	NS
	2 Years Postoperative	Mean	0.80	0.78	
		Median	0.80	0.80	NS

CI = cochlear implantation, HUI = health utilities index, EQ-5D = EuroQol-5D, TTO = time trade-off, VAS = visual analogue scale, NS = not significant (p>0.05)

Figure 1 | Cost-utility analyses



HUI = health utilities index, TTO = time trade-off, VAS = visual analogue scale,
ICUR = incremental cost-utility ratio, QALY = quality adjusted life year, WTP = willingness to pay

DISCUSSION

With this study, we have shown that simultaneous bilateral CI becomes a cost-effective intervention in postlingually deafened adults after a period of 5-10 years of bilateral implant use, based on the HUI3, TTO and VAS on hearing. Based on the EQ-5D and VAS on general health results, a second implant would not be cost-effective.

Strengths and weaknesses

The strengths of our study are: 1. The outcomes are based on the results of a multicenter RCT and we were able to use real-life prospectively gathered data, instead of retrospective findings [11] or data gathered from fictional scenarios on which proxies were asked to reflect [12-14]. 2. We used 2 years of follow-up data and found little differences between the two, which shows that the results were consistent and not likely to change rapidly after implantation. Possible weaknesses are: 1. That we were not able to perform a bottom-up procedure by multiplying health units with costs per unit, since this information is not publically accessible. We decided that a top-down procedure, based on passenger prices would give a more accurate representation of reality than using reference prices per unit. As a consequence of the top-down approach, we were not able to apply sensitivity analyses for the price reduction of a second cochlear implant, which is in general 25% in most European countries, or for possible revision surgery (7.6%) or failure rates (5.1%) [15], 2. For bilateral CI cost estimation, we doubled the unilateral fees, which is an overestimation. Bilateral surgery takes longer and patients will need twice as many processor replacements for the rest of their lives, but the number of hospital visits and duration of hospital admission periods were equal in both groups. A lower price for a second cochlear implant would, however, have a positive effect on the cost-utility analysis and bilateral CI would become cost-effective even earlier than we calculated. 3. The number of participants in this study is rather small and we only included postlingually deafened adults. Using a homogenous group increases the reliability of the study, but the results are not applicable for children or prelingually deafened adults. 4. We realize that this study is mainly applicable for the Dutch population. The study participants may be comparable to CI users in other Western countries, but worldwide, there is a large variance in health care costs and travel expenses. It is therefore difficult to externalize our results to different countries. In order to get a more detailed impression of total costs and to make it more interesting for health care providers from abroad, we added

information on hospital visits, travel expenses, duration of operations, and duration of hospital admission periods. In this way, our paper can guide other researchers to apply similar analyses to their own national or regional situation.

We did not apply differential discounting. Discounting is controversial and often, equal discount rates to cost and utility are applied [16]. In this manner, ICURs remain stable [1,17]. Sensitivity analyses and discounting rates are regularly applied in literature to reduce ICURs to prove that an intervention is cost-effective, when it would not be, based on the actual outcomes of a study. These methods lead to uncertainties that we avoided by limiting sensitivity analyses and discounting.

Comparison with literature

In 2002, Summerfield et al. conducted a scenario analysis to compare cost-utility of simultaneous bilateral CI with unilateral CI and no implantation. They recruited 70 normal hearing subjects, who answered the TTO questionnaire after reading vignettes describing the state of: 1. Being deaf with no implant, 2. Having one cochlear implant, or 3. Having bilateral implants. Modeled for a 30-year period, they found a cost-utility ratio per QALY of £61,734 for bilateral versus unilateral implantation [12]. Other studies mostly describe the cost-utility of a sequentially rather than simultaneously implanted second CI. The RCT performed by Summerfield et al. (2006) included 24 postlingually deafened adults who received a second implant at the beginning of the study, or after a 12 month-delay. Although sequential bilateral implantation led to significant improvement in self-reported measures of spatial hearing, quality of hearing and hearing for speech (SSQ), bilateral implantees showed neutral or negative changes on general QoL questionnaires (GHSI, HUI3, VAS, EQ-5D) after receiving a second implant. A second implant did not appear to be cost-effective, when modeled for a 30-year period [18]. Chen et al. (2014) estimated the benefits of bilateral CI by creating three scenarios on which patients (deaf patients without cochlear implants, unilateral implantees and bilateral implantees) and health professionals were asked to reflect by completing HUI3 questionnaires. The scenarios comprised: 1. Deafness without intervention, 2. Unilateral CI and 3. Bilateral CI. They found an ICUR of $55,020/QALY from unilateral to bilateral CI, over 25 years [14]. Bichey et al. (2008) performed a retrospective cohort study and asked 23 bilaterally implanted adults to complete the HUI3 questionnaire for their everyday situation with two implants, and assuming

they still had only one implant. They concluded that a second implant would be cost-effective, when modeled for a life expectancy of 76 years [11].

In this study, simultaneous bilateral CI appeared to be cost-effective after 5-10years of use, based on the questionnaires that comprised questions on hearing (HUI3, TTO and VAS on hearing), even if utility scores were not significantly higher in the bilateral than unilateral group. A second implant was not cost-effective, based on general QoL questionnaire results (EQ-5D and VAS on general health).

Overall, we found lower ICURs for (simultaneous) bilateral implantation than described in the literature even though our cost estimation was relatively high, since we used passenger prices and did not apply discounting rates or differential sensitivity analyses, except from modeling for different periods of time. This is the first study that describes a cost-utility analysis to compare unilateral with simultaneous bilateral CI in postlingually deafened adults, based on a multicenter RCT.

REFERENCES

1. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. *Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen,* 2011; Geactualiseerde versie 2010.

2. Kuthubutheen J, Mittmann N, Amoodi H, Qian W, Chen JM. The effect of different utility measures on the cost-effectiveness of bilateral cochlear implantation. *Laryngoscope* 2015;125(2):442-7.

3. Shiroiwa T, Igarashi A, Fukuda T, Ikeda S. WTP for a QALY and health states: More money for severer health states? *Cost Effectiveness and Resource Allocation* 2013; 11:22.

4. van Gils PF, Schoemaker CG, Polder JJ. Stand van zaken. Hoeveel mag een gewonnen levensjaar kosten? Onderzoek naar de waardering van de QALY. *Ned Tijdschr Geneeskd* 2013; 157: A6507.

5. Bobinac A, Van Exel NJ, Rutten FF, Brouwer WB. Willingness to pay for a quality-adjusted life-year: the individual perspective. *Value Health*. 2010; 13(8):1046-55.

6. Lammers MJW, Grolman W, Smulders YE, Rovers MM. The cost-utility of bilateral cochlear implantation: a systematic review. *Laryngoscope* 2011;121:2604-9.

7. Feeny D, Furlong W, Torrance GW, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. *Med Care* 2002; 40:113–28.

8. Torrance GW. Measurement of health state utilities for economic appraisal, a review. *J Health Econ* 1986; 5:1-30.

9. Brooks R. EuroQol: the current state of play. *Health Policy* 1996; 37: 53–72.

10. Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, van Busschbach JJ. Measuring the quality of life in economic evaluations: the Dutch EQ-5D tariff. *Ned Tijdschr Geneeskd* 2005; 149: 1574–8.

11. Bichey BG, Miyamoto RT. Outcomes in bilateral cochlear implantation. *Otolaryngol Head Neck Surg* 2008;138:655–61.

12. Summerfield AQ, Marshall DH, Barton GR, Bloor KE. A cost-utility scenario analysis of bilateral cochlear implantation. *Arch Otolaryngol Head Neck Surg*. 2002; 128(11):1255-62.

13. Summerfield AQ, Lovett RE, Bellenger H, Batten G. Estimates of the costeffectiveness of pediatric bilateral cochlear implantation. *Ear Hear* 2010; 31:611–624.

14. Chen JM, Amoodi H, Mittmann N. Cost-utility analysis of bilateral cochlear implantation in adults: a health economic assessment from the perspective of a publicly funded program. *Laryngoscope* 2014; 124(6):1452-8.

15. Wang JT, Wang AY, Psarros C, Da Cruz M. Rates of Revision and Device Failure in Cochlear Implant Surgery: A 30-Year Experience. *Laryngoscope* 2014; 124(10):2393-99.

16. NICE. Guide to the Methods of Technology Appraisal. NICE: London, April 2004.

CHAPTER 05

Objective and subjective spatial hearing results in bilateral and unilateral cochlear implantation

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ABSTRACT

Objectives

Sound perception and localization are frequently evaluated skills in cochlear implant (CI) users. They can be measured objectively in a laboratory test setting or by administering questionnaires (subjectively). Regular evaluation is important in this era, in which eligibility criteria for (bilateral) cochlear implantation and possibilities of CIs are changing constantly. In this article, we will describe correlations between subjective and objective results on sound perception and localization tests, in both unilateral and bilateral CI users.

Study Design

This study is part of a randomized controlled trial (RCT), in which 38 postlingually deafened adult patients participated. Nineteen patients had received a unilateral CI and 19 had received bilateral CIs.

Methods

We analyzed the correlations between the Speech, Spatial and Qualities Hearing Scale (SSQ) and Nijmegen Cochlear Implant Questionnaire (NCIQ) on the one hand, and objectively measured speech perception and localization skills on the other hand. The objective tests were conducted with the Advanced Bionics-York Crescent of sound and the 1-year follow-up results were used.

Results

Although we found several significant correlations between the subjective and objective tests, this was particularly the case in bilaterally implanted CI users. The SSQ and NCIQ results in the unilateral group did not correlate well with the objective results.

Conclusions

Objective and subjective tests both have their advantages and disadvantages. This study shows that there are large discrepancies in correlations between unilaterally and bilaterally implanted patients. Because of the inconsistencies in correlations, the two tests cannot substitute each other and should both be carried out for proper evaluation of cochlear implantation.

INTRODUCTION

Cochlear implantation is a successful treatment for profound to severe perceptive hearing loss. Although unilateral cochlear implantation (UCI) still is the standard treatment in most countries, an increasing amount of patients worldwide is being implanted bilaterally, in order to improve (spatial) hearing skills, speech understanding in noise and for the reduction of tinnitus [1,2]. For the same reasons, the interest in implanting patients with a unilateral hearing loss is growing. It is well known that bilateral hearing has several advantages over unilateral hearing. With two functioning ears, one is able to localize sounds, which is very difficult for people with only one functioning ear. Also, hearing with two ears enables one to better-differentiate speech from background noise than with one ear [3-6]. These are both important aspects in everyday listening situations. The criteria for (bilateral) implantation are changing constantly and the quality and possibilities of cochlear implants are growing. In order to keep up with these changes and to provide best clinical practice, most cochlear implant (CI) centers evaluate the hearing results of their cochlear implantees on a regular basis. Hearing skills can be tested in a laboratory setting (objectively), or by administering questionnaires (subjectively). Objective tests are, over all, robust and reliable, but time-consuming. Also, it is known that objective outcomes do not always reflect patients' own experiences [7-9]. Questionnaires on the other hand, are easy to administer and a large set of data can be gathered in a short period of time. However, questions can be misinterpreted and missing values easily occur when patients do not fill out (part of) the questionnaires. The Nijmegen Cochlear Implant Questionnaire (NCIQ) [10] and Speech, Spatial and Qualities Hearing Scale (SSQ) [11] are questionnaires that can be used to measure different aspects of hearing, like speech understanding in noise and sound localization. In literature on unilateral or bimodal implantation (CI with contralateral hearing aid (HA)), the results on these questionnaires did not correlate well with objective laboratory findings [7-9]. Not much is known about the correlation between objective and subjective outcomes in bilateral CI users.

In this study, we will assess correlations between objective and subjective test results in both unilateral and bilateral adult cochlear implantees.

MATERIALS AND METHODS

Study design and participants

This study was part of a multicenter randomized controlled trial (RCT) on the benefits of simultaneous bilateral cochlear implantation (BiCI) compared to UCI in adults with profound to severe bilateral postlingual perceptive hearing loss. The study was approved by the Human Ethics Committees of all participating centers (NL2466001808) and registered in the Dutch Trial Register (NTR1722). Between January 2010 and September 2012, we included 38 adults in this study. Using a web-based randomization program, subjects were randomized to either 1) UCI or 2) simultaneous BiCI. All participants were implanted with Advanced Bionics HiRes90K® implants. The use of a contralateral hearing aid was encouraged for the unilateral implantees. Details of the study population are presented in Table 1.

Table 1 | Patient characteristics

	UCI	BiCI	p-value
Male:Female	11:8	8:11	NS
Age at inclusion (yrs)	52.5 (12.5) [26-67]	47.7 (15.9) [18-70]	NS
Age start severe hearing loss AD (yrs)	30.8 (20.1) [3-55]	30.5 (17.2) [3-63]	NS
PTA AD (dB)	106.3 (12) [78-125]	106.1 (16) [80-130]	NS
PTA AS (dB)	107.5 (13) [83-127]	108.3 (18) [77-130]	NS
Max. phoneme score	46.2 (20.4) [0-80]	42.1 (27.6) [0-90]	NS
With hearing aids (%)	46.2 (20.4) [0-80]	42.1 (27.6) [0-90]	NS
Treatment Hospital			NS
Utrecht	11	8	
Maastricht	4	5	
Nijmegen	2	3	
Leiden	1	2	
Groningen	1	1	
Hearing aid use before CI			0.04
Yes	19	15	
No	0	4	

Mean (standard deviation) [range]. UCI = unilateral cochlear implantation, BiCI = Bilateral cochlear implantation, NS = not significant, AD = right ear, AS = left ear, PTA (pure tone audiogram) - average at 0.5, 1 and 2 kHz. The items in bold are made up of the values associated with the sub-items below them. A significance value is given alongside the item in bold.

In this article, we will present the subjective and objective hearing results measured one year after implantation.

Subjective hearing

Self-reported (subjective) benefits in everyday listening situations were assessed with the following questionnaires:

1. Speech, Spatial and Qualities Hearing Scale (SSQ). This questionnaire consists of three chapters of questions. Participants were asked to rate their hearing capabilities on a 0-10 scale (0= not capable at all, 10=perfectly capable). The SSQ1 comprises questions on speech understanding in silence, in background noise, in resonating environments and on the telephone. The SSQ2 comprises questions on spatial hearing; identifying directions of sounds and distance approximation, and the SSQ3 encompasses questions on the quality of hearing [11].
2. Nijmegen Cochlear Implant Questionnaire (NCIQ). This questionnaire contains six subdomains of hearing that are rated categorically (0-5 (never-always) and "not applicable"). The subdomains are 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 [10].

Objective hearing tests

Speech-intelligibility-in-noise and sound localization tests were conducted with the Dutch version of the AB-York crescent of sound. The test battery included the U-STARR (Utrecht Sentence Test with Adaptive Randomized Roving levels)), the speech-intelligibility test with spatially separated sources (SISSS), and a sound localization test [12]. With the U-STARR, sentences were presented in noise, both coming from straight ahead. The sentences were presented at 65, 70 or 75 dB SPL (randomly selected), in noise with an adaptive level. The outcome was the signal-to-noise ratio (SNR) average of the last ten sentences, which is the speech reception threshold in noise (SRTn). For the SISSS, the same procedure was used as for the U-STARR. The only difference was that the sentences were presented from 60° to the left (-60° azimuth) or to the right (+60° azimuth) of the subject and the noise was presented from 60 degrees at the opposite side. For the sound localization test, a phrase 'Hello what's this?' was randomly presented from loudspeakers at 0°, ±15°, ±30° and ±60° angles, 30 times per condition. Again, the phrase was randomly presented at 60, 65, or 70 dB SPL. The result was the percentage

of correct responses with a 60°, 30° or 15° angle between speakers [12]. All tests were performed in three listening conditions: 1. monaurally, with either one of the CIs or the HA switched on, 2. bilaterally, using both cochlear implants, and 3. bimodally, with both CI and HA switched on (when using a contralateral HA). In the unilateral group, patients were encouraged to use a contralateral hearing aid. In order to compare bilateral implantation to the next best option, we defined a "patient's preferred situation" for each patient in the unilateral group. This was their daily hearing situation; either wearing the cochlear implant only or an implant and hearing aid. Results from the bilateral group were compared to results of the "patient's preferred situations" from the unilateral group. When sounds come from different directions, patients usually have a "best hearing situation" and a "worst hearing situation". A patient's "best hearing situation" occurs when sound is presented to the best hearing ear and noise to the worst hearing ear. In the unilateral group, the best hearing ear is the implanted ear. In the bilateral group, patients usually also have one ear with which they hear (slightly) better than with the other. We defined the "best performing situation" and "worst performing situation" for each patient.

Comparison of subjective and objective tests

We calculated correlations between subjective and objective test results for the whole study group and for the unilateral and bilateral group separately.

Statistical analysis

In order to compare baseline characteristics, we used the student's *t*-test for numeric, normally distributed data and the chi square test for ordinal data. None of the objective and subjective test results were normally distributed. For this reason we present median results and ranges. In order to compare the objective results and SSQ scores between the unilateral and bilateral group, we used the Mann-Whitney U-test. For the NCIQ we used the chi square test. To measure the correlation between the objective and subjective test results we calculated the spearman rho correlation coefficient (r). A correlation of <0.19 is considered very weak, 0.20-0.39 weak, 0.40-0.59 moderate, 0.60-0.79 strong, >0.80 very strong. The same counts for identical, but negative values. In the speech-in-noise tests (U-STARR and SISSS), a low result indicates good performance, while in the localization tests and subjective tests, a high score indicates good performance. For this reason, when speech-in-noise results are compared with

subjective outcomes, correlations are often negative. All data were analyzed using SPSS 21.0 and a p-value <0.05 was considered significant.

RESULTS

Subjective results

One year after implantation, the BiCI group showed significantly better results on the SSQ1, SSQ2 and SSQ3 than the UCI group ($p<0.05$). On the NCIQ, the BiCI group reported better hearing capabilities, although they did not differ significantly from the UCI group ($p>0.05$) (cf. Figure 1).

Objective results

At the 1-year follow-up test moment, there was no significant difference between groups on the U-STARR ($p>0.05$). On the SISSS, when sound was presented to the non-implanted ear and noise to the implanted ear ("worst hearing situation"), the UCI group performed significantly worse than the BiCI group in their "worst hearing situations" ($p<0.05$). When sound was presented to the implanted ear and noise to the non-implanted ear ("best hearing situation"), the unilateral implantees performed similar to the bilateral implantees in their "best hearing situations" ($p>0.05$). Localization of sounds was difficult for unilaterally implanted subjects and they performed significantly worse than the unilateral implantees on all 3 localization tests ($p<0.05$) (cf. Figure 1).

Figure 1 | Subjective and objective test results

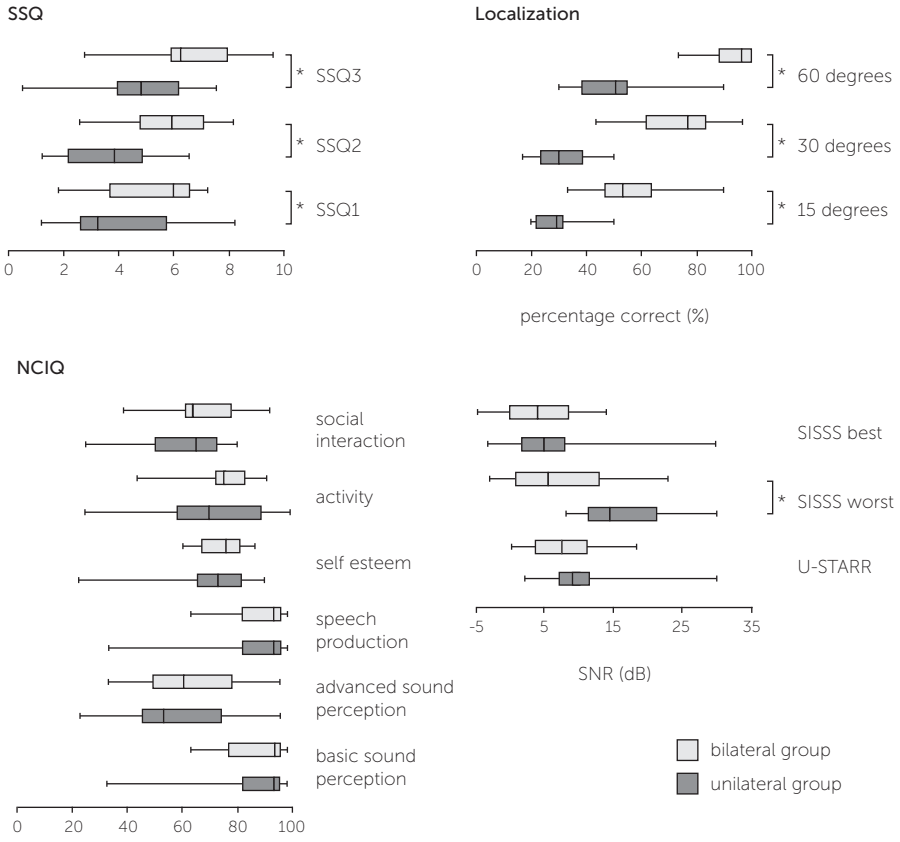

Figure 1 shows the subjective outcomes on the left side (SSQ and NCIQ) and the objective outcomes (localization SISSS test and U-STARR) on the right side, for both bilaterally (n=19) and unilaterally (n=19) implanted subjects.

* = $p<0.05$. The X-axis of the SSQ represents questionnaire results on a 0-10 scale. The X-axis of the NCIQ represents questionnaire results on a 0-100 scale.

CORRELATIONS

Subjective versus objective sound perception

There were ample significant correlations between the objective and subjective test results when all 38 patients were included (cf. Table 2). The correlations were predominantly weak to moderate. They were negative, because a high outcome (SRTn) on the U-STARR or SISSS indicates bad performance, while a high outcome on a questionnaire indicates good self-reported performance. There were significant correlations between the U-STARR on the one hand and SSQ1, SSQ3, and 3 NCIQ subdomains (advanced sound perception, activity limitations and social interaction) on the other hand. We found significant correlations between the SISSS (worst hearing situation) on the one hand and SSQ1, SSQ2, SSQ3 and 3 NCIQ subdomains (basic sound perception, advanced sound perception and speech) on the other hand. Furthermore, there were significant correlations between the SISSS (best hearing situation) on the one hand and the SSQ1, SSQ3 and 3 NCIQ subdomains (advanced sound perception, activity limitations and social interactions) on the other hand (cf. Table 2).

Sub analyses of the bilateral and unilateral group showed that correlations were stronger in the BiCI group (moderate – strong) than in the UCI group (very weak – moderate) or in the whole group (weak – moderate). The majority of the correlations were not significant in the UCI group (cf. Table 2).

Table 2 | Spearman's rho correlation coefficient (r). Subjective versus objective sound perception tests

Correlation Objective versus subjective outcomes									
Speech in noise	**U-STARR**			**SISSS_worst case**			**SISSS_best case**		
	Whole group	UCI	BiCI	Whole group	UCI	BiCI	Whole group	UCI	BiCI
	n=38	n=19	n=19	n=38	n=19	n=19	n=38	n=19	n=19
SSQ1 (Speech in silence and noise)	**-0.38***	-0.25	-0.50*	**-0.35***	-0.18	-0.30	**-0.38***	-0.27	-0.43
SSQ2 (Spatial hearing)	**-0.26**	-0.23	-0.27	**-0.47****	-0.20	-0.31	**-0.24**	-0.09	-0.37
SSQ3 (Quality of hearing)	**-0.41***	-0.48*	-0.39	**-0.47****	-0.44	-0.30	**-0.38***	-0.48*	-0.32
NCIQ_basic	**-0.23**	-0.07	-0.46*	**-0.34***	-0.24	-0.48*	**-0.26**	0.17	-0.58*
NCIQ_advanced	**-0.47****	-0.43	-0.55*	**-0.40***	-0.39	-0.46*	**-0.46****	-0.34	-0.51*
NCIQ_speech	**-0.25**	-0.07	-0.49*	**-0.37***	-0.24	-0.51*	**-0.29**	0.17	-0.61**
NCIQ_ self esteem	**-0.32**	-0.15	-0.58*	**-0.28**	-0.12	-0.44	**-0.21**	0.2	-0.50*
NCIQ_activity limitations	**-0.37***	-0.38	-0.47*	**-0.30**	-0.23	-0.37	**-0.38***	-0.16	-0.57*
NCIQ_social interaction	**-0.40***	-0.31	-0.47*	**-0.30**	-0.19	-0.25	**-0.34***	-0.11	-0.44

** = p <0.01, * = p <0.05, r <0.19 = very weak, r 0.20-0.39 = weak, r 0.40-0.59 = moderate, r 0.60-0.79 = strong, r >0.80 = very strong. UCI = Unilateral Cochlear Implantation. BiCI = Bilateral Cochlear Implantation. U-STARR = Utrecht- Sentence Test with Adaptive Randomized Roving levels. SISSS = speech-intelligibility test with spatially separated sources (SISSS), SSQ = Speech, Spatial and Qualities hearing scale. NCIQ = Nijmegen CI Questionnaire.

Subjective versus objective localization tests

There were several significant correlations between the objective localization tests and the SSQ. When all 38 participants were included, there was a significant correlation between the SSQ2 (spatial hearing) and all 3 localization tests (moderate – strong correlations). The SSQ3 (quality of hearing) correlated significantly with the 60° and 30° localization tests (moderate and weak correlation respectively) and the SSQ1 with the 60° test only (weak correlation). Most of the correlations were not significant in the BiCI group and none of them were significant in the UCI group (cf. Table 3). The correlations in the UCI group were (very) weak.

Table 3 | Spearman's rho correlation coefficient (r). Subjective versus objective sound localization tests.

	60degrees			30 degrees			15degrees		
	Whole group	UCI	BiCI	Whole group	UCI	BiCI	Whole group	UCI	BiCI
	n=38	n=19	n=19	n=38	n=19	n=19	n=38	n=19	n=19
SSQ1 (Speech in silence and noise)	**0.34***	-0.16	0.42	**0.31**	-0.30	0.26	**0.32**	-0.16	0.20
SSQ2 (Spatial hearing)	**0.63****	0.03	0.64**	**0.59****	-0.05	0.45	**0.50****	0.08	0.43
SSQ3 (Quality of hearing)	**0.42****	-0.12	0.38	**0.39***	-0.35	0.30	**0.31**	-0.25	0.21

** = p<0.01, * = p<0.05, r <0.19 = very weak, r 0.20-0.39 = weak, r 0.40-0.59 = moderate, r 0.60-0.79 = strong, r >0.80 = very strong. UCI = Unilateral Cochlear Implantation. BiCI = Bilateral Cochlear Implantation. SSQ = Speech, Spatial and Qualities hearing scale.

DISCUSSION

In this study, we examined correlations between objective and subjective test results in adult CI users. We performed sub group analyses for bilateral and unilateral cochlear implantees. Our aim was to investigate if CI-users' objectively measured sound perception and localization capabilities corresponded to the self-reported questionnaire outcomes on the same aspects of hearing. There was a significant correlation between the U-STARR and the SSQ1 and NCIQ (advanced sound perception), in the whole study group and in the BiCI group, but not the UCI group. This means that bilateral implantees' self reported skills corresponded better to speech-in-noise- and advanced sound perception capabilities than those of the UCI group. The correlations between the SISSS (best hearing situation and worst hearing situation) and the SSQ1 were weak, but significant for the whole study group. They were however, not significant in the BiCI group or the UCI group. We found strong correlations between the localization tests and the SSQ2 in the whole study group and the BiCI group. The correlations between these tests were surprisingly low in the UCI sub group.

Comparison with literature

Hirschfelder et al. (2008) studied 62 postlingually deafened unilaterally implanted adults. They found a significant correlation between the NCIQ (advanced sound perception subdomain) and the Freiburger monosyllable test in quiet (r=0.43) and between this subdomain and the HSM sentence test in noise (r=0.45) [8]. Damen et al. (2007) studied 69 postlingually deafened adult patients (59 unilaterally implanted and 10 not implanted) and found a significant positive correlation between the total NCIQ and Antwerp-Nijmegen (AN) syllable test (in silence) (r=0.48) and NVA phoneme score (in silence) (r=0.32). The NCIQ did not correlate with the AN spondee results (in silence) or NVA word scores (in silence) [7]. In agreement with the literature, we found weak to moderate correlations (r=-0.34 - -0.43) between the NCIQ (advanced sound perception) and speech-in-noise tests in the UCI group, although not significant. Heo et al (2013) studied 14 postlingually deafened adults with a unilateral CI and a contralateral hearing aid. They performed a localization test and a speech recognition and environmental sound recognition test in noise. They compared these objective findings with self-reported Korean-SSQ results. They found a significant correlation between the SSQ2 and environmental sound localization (r=0.57), and environmental sound identification (r=0.55). The SSQ1 and SSQ2 did not correlate with the other objective tests [9]. In contrast to the study of Heo et al., we found negligible correlations between the objective and subjective localization tests in the UCI group. Sparreboom et al. (2012) investigated correlations between the parent-proxy version of the SSQ, NCIQ and speech in noise and localization tests in 30 prelingually deafened children who underwent sequential bilateral implantation. Like in our postlingually deafened adult BiCI group, they found a significant correlation between the localization test and SSQ. They did not find a significant correlation between speech perception in noise and SSQ or NCIQ, which we did in our BiCI group [13].

Strengths and weaknesses

The major strength of this study is that it is part of an RCT and that the participants had been randomly allocated to the UCI or BiCI group. For this reason, an allocation bias had not occurred and the two groups were alike at baseline. All participants had completed the questionnaires one year after surgery and had performed the objective tests within the same week. None of the participants were lost to follow-up and we did not have any missing data. A weakness of the study is that the study groups were rather

small, which became clear when we performed the sub group analyses. Compared to the literature, however, the amount of participants was substantial.

CONCLUSION

This study is the first to report correlations between subjective and objective findings in bilaterally implanted patients, measured in a RCT setting. Interestingly, we found large discrepancies between the BiCI group and UCI group. The self-reported hearing capabilities in the former corresponded much better to the objective test results than in the latter. Since objective and subjective results do not necessarily correlate with each other, questionnaires cannot substitute objective laboratory tests. In order to evaluate hearing capabilities of (bilateral) cochlear implantees on a regular basis, both objective and subjective tests should be performed.

REFERENCES

1. Schoonhoven van J, Sparreboom M, Zanten van GA et al. The Effectiveness of Bilateral Cochlear Implants for Severe-to-Profound Deafness in Adults: A Systematic Review. *Otol Neurotol* 2013;34(2):190-8.

2. van Zon A, Smulders YE, Ramakers GG, Stegeman I, Smit AL, Van Zanten GA, Stokroos RJ, Hendrice N, Free RH, Maat B, Frijns JH, Mylanus EA, Huinck WJ, Topsakal V, Tange RA, Grolman W. Effect of unilateral and simultaneous bilateral cochlear implantation on tinnitus: A randomized controlled trial. *Laryngoscope* 2015 Aug 8.

3. Middlebrooks JC, Green DM. Sound localization by human listeners. *Ann Rev Psychol* 1991;42:135-59.

4. Bronkhorst AW, Plomp R. The effect of head-induced interaural time and level differences on speech intelligibility in noise. *J Acoust Soc Am* 1988;83:1508-16.

5. Dirks DD, Wilson RH. The effect of spatially separated sound sources on speech intelligibility. *J Speech Hear Res* 1969;12:5-38.

6. MacKeith NW, Coles RRA. Binaural advantages in hearing of speech. *J Laryngol Otol* 1971; 85:213-32.

7. Damen GW, Beynon AJ, Krabbe PF, Mulder JJ, Mylanus EA. Cochlear implantation and quality of life in postlingually deaf adults: long-term follow-up. *Otolaryngol Head Neck Surg.* 2007;136(4):597-604.

8. Hirschfelder A, Gräbel S, Olze H. The impact of cochlear implantation on quality of life: the role of audiologic performance and variables. *Otolaryngol Head Neck Surg.* 2008;138(3):357-62.

9. Heo JH, Lee JH, Lee WS. Bimodal benefits on objective and subjective outcomes for adult cochlear implant users. *Korean J Audiol.* 2013;17(2):65-73.

10. Hinderink JB, Krabbe PFM, Broek van den P. Development and application of a health-related qualityof-life instrument for adults with cochlear implants: The Nijmegen Cochlear Implant Questionnaire. *Otolaryngol Head Neck Surg* 2000;123:756-65.

11. Gatehouse S, Noble W. The Speech, Spatial and Qualities of Hearing Scale (SSQ). *Int J Audiol* 2004;43:85–99.

12. Smulders YE, Rinia AB, Pourier VEC, Van Zon A, Van Zanten GA, Stegeman I, Scherf FWAC, Smit AL, Topsakal V, Tange RA, Grolman W. Validation of the U-STARR with the AB-York Crescent of Sound, a New Instrument to Evaluate Speech Intelligibility in Noise and Spatial Hearing Skills. Audiol Neurotol Extra 2015;5:1-10.

13. Sparreboom M, Snik AF, Mylanus EA. Sequential bilateral cochlear implantation in children: quality of life. *Arch Otolaryngol Head Neck Surg*. 2012;138(2):134-41.

CHAPTER 06

What is the effect of time between sequential cochlear implantations on hearing in adults and children? A systematic review of the literature.

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Laryngoscope. 2011 Sep;121(9):1942-9

ABSTRACT

Objective

Bilateral cochlear implantation is a safe and effective intervention for severe sensorineural hearing loss and is believed to be more effective than unilateral implantation. This review article investigates the effect of time between sequential cochlear implantations on hearing results in both adults and children.

Study Design

Systematic review of cohort studies.

Methods

We searched Pubmed, EMBASE and CINAHL from inception to 16 August 2010 using the terms hearing loss, cochlear implant, delay and their synonyms.

Results

Eleven studies evaluating the effect of time between sequential cochlear implantations on hearing performance were included. Although the quality of studies was poor due to a significant risk of bias, all studies reported that auditory performance is better in a bilateral listening situation than with either one cochlear implant activated unilaterally. Five studies discussed postlingually deafened adults. In four, bilateral hearing was not affected by the amount of time between implantations. One study did report a negative effect of delay on speech intelligibility in silence. Seven studies discussed prelingually deafened children. None reported a negative effect of inter implantation delay on sound localization performance. One study reported poorer results after extended intervals on speech intelligibility in silence and two in noise.

Conclusion

Current evidence suggests that a second implant can be beneficial even after a substantial interval between sequential implantations. The quality of the evidence is, however, rather poor and to confirm this postulation, high quality trials assessing the effectiveness of a second cochlear implant after a time delay should be initiated.

INTRODUCTION

Bilateral cochlear implantation (BICI) is growing in popularity for the treatment of severely deafened adults and children. There are three motivations for bilateral implantation: (1) to ensure that best ear is stimulated, (2) to provide a backup in the event of device failure and (3) to create the potential for binaural hearing and benefit from its perceptive effects: 'head shadow effect', 'summation effect' and 'squelch effect' [1-4].

Previous studies, that compared unilateral with bilateral cochlear implantation, showed that auditory outcomes are better for bilateral than unilateral listening situations. The addition of a second cochlear implant (CI) leads to better performance in difficult-listening situations such as selective listening to a sound of interest in noisy conditions and localization of sounds [1,2,5]. Moreover, binaural hearing is believed to play a key role in the development of language and speech in children [1-3].

In general, simultaneous bilateral cochlear implantation is believed to be preferential over sequential implantation. Simultaneous implantation prevents the occurrence of timing differences of brainstem activity that may develop in the case of prolonged unilateral CI usage and may compromise the development of binaural hearing in infants [4,6].

While the interest in BICI is growing among unilaterally implanted patients and their caregivers, new questions arise. Is bilateral cochlear implantation beneficial, even if there is a delay between the placement of the first and second CI? How long after unilateral cochlear implantation can a second CI contribute to improved hearing?

The objective of this study therefore is to systematically review the literature on sequential cochlear implantation in both adults and children in order to answer the following question: what is the effect of inter implantation delay on sound localization and speech intelligibility performance in silence and in noise?

MATERIALS AND METHODS

Search strategy

In order to identify articles reporting on a time delay between the first and second cochlear implant, we searched Pubmed, EMBASE and CINAHL from inception to 16 August 2010 using the terms hearing loss, cochlear implant, delay and their synonyms (see Appendix for complete search strategy). In addition, a reference and related article search was performed.

Study selection

We screened titles and abstracts without blinding to authorship or journal. Potentially relevant studies were obtained and the full text examined. Criteria for in and exclusion are shown in figure 1. We searched for studies that involved sequential bilateral implanted subjects in which the effect of a delay between surgeries on test results was analyzed. The outcomes of interest were: speech intelligibility in silence or noise and sound localization. We excluded papers if the authors did not analyze the effect of interval.

The quality of a study depends on the limitation of bias: selection bias, performance bias, attrition bias, detection bias and reporting bias (based on a common classification scheme for bias, recommended by the Cochrane Collaboration) [7]. We therefore used the following criteria for quality assessment: 1. Was the allocation of intervention assignment concealed? (Were participants blindly assigned to a certain treatment group?) 2. Were patients, caregivers and outcome assessors blinded? 3. Follow up: Had participants gained equal bilateral listening experience at the moment of testing?; Were any of the participants lost to follow up before the end of the study? 4. Did selective reporting of data occur (no explanation of missing data)? 5. Were there any other sorts of bias the authors did not account for? The quality assessment is summarized in table 1.

Data extraction and statistical analysis

We extracted the following data from each study: 1. Study characteristics: study design, number of participants, tests performed, age, duration of deafness and time interval between implantations; 2. Study outcomes: test characteristics, outcomes with the first CI (CI1), second CI (CI2) and both CIs activated simultaneously and statistical differences between unilateral and bilateral performance.

Study characteristics are presented in table 2 and 4. Authors presented their data in different manners. In order to give an overview of comparable information, we extracted data from graphs or computed them from data presented in tables in those cases where specific numbers were not given by the authors. Extracted numbers are indicated by an asterisk.

Due to large heterogeneity between the studies included, pooling of data was not possible. We therefore summarized the outcomes per study (cf. Table 3 and 5). Some studies carried out more tests than presented in the tables. If authors failed to analyze the effect of interval on test outcomes, we excluded these results from the tables.

Results

Our initial search generated a total of 703 possible relevant titles. After removal of duplicates, 438 titles remained. Titles, abstracts, and full-text articles were consecutively screened for the in- and exclusion criteria (cf. Figure 1). Eleven papers were included in this review. Six studies reported on children's results and mainly involved prelingually deafened children. Four papers reported on adults' results and all involved postlingually deafened patients. One article reported on both prelingually deafened children and postlingually deafened adults.

The quality of the papers is summarized in table 1. All studies were patient series and the data were mainly gathered retrospectively. Randomization or blinding did not take place in any of the studies. In four out of eleven studies, participants were tested after an equal amount of bilateral listening experience. In the other studies, this amount of experience could vary to up to four years. Since most studies reported retrospectively gained data, loss to follow up did not occur in most studies. In other studies in which patients were tested repeatedly, figures did not contain data of all participants, while the authors failed to explain these missing data. Other factors that could bias the results were: 1. Electrode insertion depth, 2. Type of cochlear implant, 3. Age at first implantation and duration of deafness before implantation, 4.Bilateral listening experience (BiCI). 5. Hearing aid experience, 6. Age at onset of hearing loss, 7. BiCI compliance. Studies were considered to be free from other bias if six or more of the seven factors above were accounted for. Table 1 displays the risk of bias for all studies.

Figure 1 | Study selection process

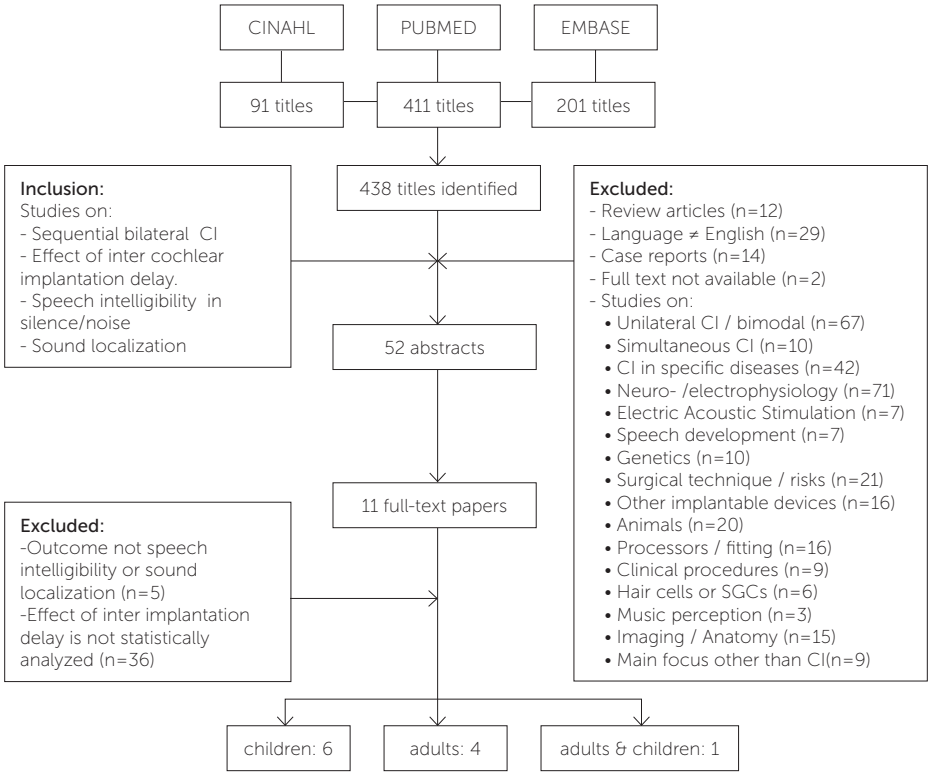


Table 1 | Patient characteristics

	Allocation	Blinding	Follow-up after equal BICI experience	Loss to Follow Up	Selective reporting	Free from other bias
Laske 2009	-	-	-	+	+	-
Zeitler 2008	-	-	+	+	+	+
Ramsden 2005	-	-	+	+	+	-
Nopp 2004	-	-	-	+	+	-
Schleich 2004	-	-	-	+	+	-
Grieco-Calub 2010	-	-	-	+	-	-
Deun 2009	-	-	-	+	+	-
Gordon 2009	-	-	+	+	+	+
Steffens 2008	-	-	-	-	-	-
Zeitler 2008	-	-	+	+	+	+
Scherf 2007	-	-	+	-	-	+
Kuhn-Inacker 2004	-	-	-	-	-	-

1. Was allocation of intervention assignment concealed?
2. Were patients, caregivers and outcome assessors blinded?
3. Were participants followed-up for a sufficient period of time, were any of them lost to follow up?
4. Did selective report of data occur?
5. Were there any other sorts of (selection) bias which the authors did not account for?

+: authors took this factor into account
-: authors did not take this factor into account or did not mention how they did this

Adults

The five studies that reported on adults included a total of 122 subjects (irrespective of about 18 subjects who participated in two studies), aged 17-82 years. Inter implantation intervals varied from 0 to 19 years.

Speech intelligibility (words or sentences) was tested in four out of five studies. Laske et al. (2009) described the results of 29 sequentially implanted adult patients with inter implantation delays of 0-19 years [8]. The first implanted ear was supposed to be the 'better ear'. However, it appeared that in 73% of the cases only, the first implanted ear remained the better performing ear after bilateral implantation. The authors demonstrated that, both in silence and in noise, patients achieved equal results with both implants switched on as with their 'better ear' only. Patients performed significantly worse with their 'poorer ear' compared to the bilateral condition. The authors showed that there was a significant positive correlation between inter implantation delay and the difference between results achieved with CI1 and CI2 individually on the Oldenburger Sentence Test (OST) in quiet. A short interval yielded better results for the second implant. Interestingly, a graph illustrating

these data showed that all 16 subjects who received their second CI within about seven years after the first one, achieved similar results with their first and second implants separately. Longer delays led to worse results acquired with CI2 alone. For the OST in noise, the authors identified a trend towards a negative effect of inter implantation delay, but this correlation was not significant

Three studies reported a benefit of bilateral cochlear implantation on speech intelligibility performance in silence and noise. None of them detected a correlation between inter implantation delay and bilateral performance or the difference between CI1 and CI2-only performance (cf. Table 3). Maximum inter cochlear implantation intervals were 7, 5.6 and 15.1years, respectively (cf. Table 2).

Sound localization was tested in one study. Patients performed significantly better than chance level when both CIs were switched on and they performed better in the bilateral situation than with either one CI only, with no effect of inter implantation delay (maximum inter implantation delay: 5.6yrs) .

Table 2 | Study characteristics, adults

Study	N	Study Design	Age yrs (SD) [range]	DOD yrs (SD) [range]	Interval yrs (SD) [range]	Test
Laske ea., Otol Neurotol 2009	29	Patient series (>6mo after CI2)	37*	5.4* (6.4)	5.6 (5.7) [0-19]	Speech intelligibility in quiet and in noise
Zeitler, Otol Neurotol 2008	22	Patient series (before and 3mo after CI2)	46.9	32,1 [3-58.3]	5.6 [1.3-15.1]	Speech intelligibility in quiet and in noise
Ramsden ea., Otol Neurotol 2005	30	Patient series (before, 1w, 3mo and 9mo after CI2)	57.5 (12.5)* [29-82]	6 (4.5)* [1-15]	3 (1.3)* [1-7]	Speech intelligibility in quiet and in noise
Nopp ea., EH 2004	20	Patient series (>1mo after CI2)	45.1 (14.5)* [17-67]	12.9 (12.7)* [3-48]	2.27 (1.9)*	Localization
Schleich ea., EH 2004	21	Patient series (>1mo after CI2)	44 (14.2)* [17-67]	12.2 (12.7)* [1-48]	2.2 (1.8)* [0-5.6]	Speech intelligibility in noise

DOD = duration of bilateral deafness before CI1

* data derived from graphs or tables

Table 3 | Effect of inter cochlear implantation delay on BICI outcome, adults

Study	Test	Statistical analysis	Effect of duration of interval between surgeries.
Laske ea., Otol Neurotol 2009	Speech intelligibility	ANOVA, multivariance analysis, multiple linear regression analysis: DOD, interimplantation interval, follow-up)	
	OST quiet (%)		Significant correlation between interval and difference between CI1 and CI2 performance. (r2 = 55%, p<0.001)
	OST noise (dB SNR)		No effect of interval duration, but there was a trend towards better performance with shorter interval
Zeitler, Otol Neurotol 2008	Speech intelligibility	Pearson product correlation: interimplant delay, age CI2, DOD CI1, DOD CI2	No correlation between interval and absolute or relative improvement in CI2.
	CNC quiet		
	HINT quiet		
Ramsden ea., Otol Neurotol 2005	Speech intelligibility	Post hoc analysis (Tukey)	No correlation between interval and difference between CI1 and CI2 performance in quiet or noise
	CNC and CUNY in quiet		
	CUNY noise		
Nopp ea., EH 2004	Localization	Pearson product correlation: interimplant delay, age onset deafness, DOD	No correlation between interval and localization accuracy
	Absolute error (°)		
Schleich ea., EH 2004	Speech intelligibility	Correlation: interimplant delay, DOD CI1, DOD CI2	No correlation between interval and binaural advantage
	OST noise (dB SNR)		

BICI = Bilateral Cochlear Implantation
OST = Oldenburger Sentence Test
CNC = Consonant-Nucleus-Consonant monosyllabic words
HINT = Hearing in Noise Test (sentences)
CUNY = City University of New York sentences in silence / noise

Children

The six studies that reported on children included a total of 223 children aged 1.5-15.2 years. Inter implantation intervals varied from 0 to 14.5 years (cf. Table 4).

Speech intelligibility (words or sentences) was measured in five studies. In general, an extensive variety of speech intelligibility tests is available for children and the choice of tests usually depends on the age of subjects to be tested. All studies reported that children achieved better results with both CIs switched on than in either unilateral condition, based on results of speech intelligibility tests in silence and noise (cf. Table 5) [6,9-12]. Nevertheless, analysis of the effect of inter implantation delay on bilateral outcomes led to different conclusions in various studies. Gordon et al. (2009) analyzed four groups of children with different inter implantation intervals (0-9.4yrs) [6]. The authors showed that CI2 performance lagged CI1 performance after a certain delay and that a second CI was not beneficial in silence when the inter implantation interval exceeded 24 months. In noise, a second CI was beneficial even after a delay of more than 24 month, although prolonged deafness (>3yrs before CI1) had a negative effect on bilateral performance [7]. Speech intelligibility in silence was tested by two studies [12,13]. In both studies, inter implantation delay (maximum 14.5 and 8.4years, respectively), was not correlated with bilateral performance. Two studies [11,12] found a negative correlation between inter implantation delay and speech intelligibility in noise test results (maximum delay 14.5 and 6.9 years, respectively), whereas two other studies reported no differences[9,13] (maximum delay 4.4 and 8.4 years, respectively).

Localization tests were conducted by three studies (cf. Table 5) [11,14,15]. All three concluded that the ability to localize sounds improved significantly in the bilateral compared to unilateral condition, regardless of the duration of interval between sequential implantations. Van Deun et al. (2010) and Grieco-Calub et al. (2010) reported that early implantation (before the age of 2 years) was an important determinant for better sound localization [14,15]. The former also mentioned hearing aid use prior to implantation as a contributing factor for better results [14]. The researchers also analyzed the effect of age at second implantation on localization performance in a subgroup of subjects who had not used hearing aids before. They found better results for children who received their second implants before the age of four years. Inter implantation delay was highly correlated to age at second implantation. The authors concluded that early

implantation of the second CI is important for binaural localization development, especially for those children in whom a hearing aid is not effective and does not provide any auditory input to the non implanted side.

Table 4 | Study characteristics, children

Study	N	Study Design	Age yrs (SD) [range]	DOD yrs (SD) [range]	Interval yrs (SD) [range]	Test
Grieco-Calub ea., EH 2010	21	Patient series (3mo-3yrs after CI2)	8.1 (2.4)	2,11 (1,8)	3.8 (1.75)	Localization
		Sub group (n=11): repeated measures: 9-21mo after visit1	[3.9-12.5]	[0.5-7]	[0.8-6.6]	
Deun ea., Audiol Neurotol 2009	30	Patient series (>11mo after CI2)	8.6	3.3 (3.2)	2.8 (1.8)	Localization
			[4.2-15.2]	[0.3-11.9]	[0.8-9.3]	
Gordon ea., Otol Neurotol 2009	58	Patient series (Repeated measures 6,	NR	1.9* (0.7)	3.1* (1.0)	Speech intelligibility in quiet and in noise
		12,18,24 and 36mo after CI2)		[0- >5.3]*	[0-9.4]*	
Steffens ea., Acta Otolaryngol 2008	20	Patient series (>3mo after CI2)	7.0 (1.6)	1.6 (0.8)	3.6 (1.4)	Speech intelligibility in noise
			[3.9-10.6]	[0.2-3.0]	[0.7-6.9]	Lateralization
Zeitler ea., Otol Neurotol 2008	43	Patient series (before and 3mo after CI2)	NR	2.3	5.2	Speech intelligibility in quiet and in noise
				[0.3-14.4]	[0.8-14.5]	
Scherf ea., Int. J. Ped ORL 2007	33	Patient series (Repeated measures:	6.2 (3.4)*	2.3* (2.1)	3.3* (2.1)	Speech intelligibility in quiet and in noise
		pre-CI2 and 1,3,6,12, 18mo after CI2)	[1.5-11.8]*	[0.2-7.6]*	[0.6-8.4]*	
Kuhn-Inacker, Int J Ped ORL, 2004	18	Patient series (> 6mo after CI2)	6.4 (1.8)		1.6 (1.3)	Speech intelligibility in noise
			[2.9-9.1]		[0-4.4]	

DOD= duration of bilateral deafness before CI1
* data derived from graphs or tables
NR = not reported

Table 5 | Effect of inter cochlear implantation delay on BICI outcome, children

Study	Test		Effect of duration of interval between surgeries
Grieco-Calub ea., EH 2010	Localization	Multiple linear regression analysis (age visit, age CI1, age CI2, hearing experience, interimplant delay, BICI experience)	No effect of interval duration on bilateral localization accuracy
Deun ea., Audiol Neurotol 2009	Localization	ANCOVA (Age CI1, age CI2 inter implant delay, BICI experience, age onset deafness, HA experience)	No effect
Gordon ea., Otol Neurotol 2009	Speech intelligiblity	Stepwise linear regression analysis (Age at CI1, DOD, interimplant delay, BICI) experience, test, test condition)	Negative effect of interval duration: 11% of speech perception change relative to CI1 is explained by delay. F=45.6, p<0.0001 0.29 ± 0.04% decrease in speech score per month of delay
	Words in quiet		
	Words in noise	No differences between degree of bilateral benefit in noise across groups with different delays	No effect of interval duration F=2.6. p>0.05
Steffens ea., Acta Otolaryngol 2008	Speech intelligiblity	Correlation between subject characteristics and performance (aetiology, age onset, Age CI1, Age CI2, Interimplant interval, Experience BICI, monarual 1 score, monaural 2 score)	Negative correlation between interval and binaural advantage when speech is presented to CI2.(r=-0.536, p=0.027)
	OLKI in noise		
	Lateralization		No correlation between interval and lateralization score (r<0.5 / p>0.05)
Zeitler ea., Otol Neurotol 2008	Speech intelligiblity	Pearson product correlation: interimplant delay, age CI2, DOD CI1, DOD CI2.	
	Words (MLNT, LNT, PBK) and sentences (HINT) in quiet		No correlation p>0.05
	HINT noise		Significant correlation between interval and CI2 performance (r=-0.514, p<0.05)
Scherf ea., Int. J. Ped ORL 2007	Speech intelligibility		
	Words in quiet	Interval - speech recognition graph	A trend cannot be observed
	Words in noise	Interval - speech recognition graph	A trend cannot be observed

Kuhn-Inacker, Int J Ped ORL, 2004	Speech intelligibility Speech in noise	Linear regression analysis: age at CI1 and interimplant delay.	No effect (F= 0.0001, p=0.97)

* data derived from graphs or tables

BICI = Bilateral Cochlear Implantation
DOD = duration of bilateral deafness before CI1
OLKI = Oldenburger Kinder Reimtest: speech and noise presented from + 45° and - 45°.
MLNT = multisyllabic lexical neighborhood test (words)
LNT = lexical neighborhood test (words)
PBK = Phonemic Balanced Kindergarten word test
HINT = Hearing in Noise Test (sentences)

DISCUSSION

The major strength of this study is that we are the first to review the effect of time between sequential cochlear implantations on bilateral hearing benefits. This is, however, an essential issue as implanting the second ear is gaining popularity among unilaterally implanted patients and their caregivers. Other strengths are that it is systematic, up to date and independent.

This systematic review shows that a variety of conclusions have been drawn regarding the effect of time delay between the first and second cochlear implant. Although study quality was poor, most studies showed that a second implant was beneficial no matter how long the interval between implantations. Some studies, however, reported a trend in favor of better speech intelligibility with shorter intervals.

Some potential limitations should also be discussed. The analysis of the effect of inter implantation delay on bilateral performance was complicated by several factors. First of all, investigation of the effect was not the main interest of all studies included [9,13,14,16,17]. Whether or not inter implantation delay had an effect on the outcome was analyzed secondarily and not discussed in detail in these papers. Hence, study designs were often unsuitable and underpowered to answer the question properly. Second, in order to examine the difference between bilateral and unilateral hearing, in most cases subjects were asked to turn off one CI. The unilateral listening situation created in this manner, cannot be compared to actual unilateral cochlear implantation, since electrode insertion trauma will have occurred in both ears and since the acute performance with only one implant switched on might be less than after some time of

habituation to that condition. Third, in several studies subjects were tested after only a few months of bilateral CI experience, while further improvement of CI2 and bilateral performance was to be expected [12,15-17]. In other studies, bilateral listening experience varied considerably between subjects [8,9,11,15-17]. However, to reach a plateau stage of binaural performance may take up to two years [13,18,19]. Fourth, statistical analysis of the effect of delay was overall limited to computing a correlation coefficient between delay and hearing results. A Pearson's correlation may indicate a relation between two factors, but does not inform one about the effect size. How much worse did subjects perform as a result of a certain inter implantation delay? As Gordon et al. (2009) and Grieco-Calub et al. (2010) did, a stepwise linear regression analysis including all possible factors of influence, would have been a better approach for investigating the effect of delay.

Fifth, there was an enormous diversity in the sorts of tests carried out, test setups, outcome measures and data presentation, which made it impossible to compare studies or pool data. Finally, not all studies considered possible confounders in analyzing the effect of inter implantation delay on bilateral performance (cf. Table 1).

The paragraph above illustrates why, at this point, the research question cannot be satisfactorily answered with the literature on hand. Larger, better-quality prospective studies are needed to investigate the effect of inter implantation delay on hearing capabilities with two CIs. Momentarily, our study group is working on a randomized controlled trial in which one group receives both CIs simultaneously while the other group receives the second implant after a two-year delay. This will give us an idea of the effect of a specific delay on hearing results. A better way to study the effect of delay would be by means of a dose finding study. As the number of sequentially implanted subjects is growing worldwide the amount of data is expanding. All factors that might have an effect on bilateral outcome should be registered carefully and subjects should be followed up on regular basis for an extensive period of time until further improvement of the second CI is no longer to be expected.

Circumstantial evidence

Although the research question cannot be answered as such, several interesting issues have come forth from the literature. Most importantly, none of the studies considered

extensive inter implantation delay a contra indication for sequential implantation. Laske et al. (2009) presented three postlingually deafened adults with particularly long inter implantation delays of 17, 18 and 19 years [8]. Although they all performed considerably worse with their second CI than with their first, all three reported subjective benefits of bilateral cochlear implantation. Tyler et al. (2009) researched seven adult patients with delays of 6-17 years between implantations. The authors did not statistically analyze the effect of a delay, but did report that all subjects showed a bilateral benefit on speech intelligibility in noise [20]. Four out of seven subjects also performed relatively well (<30 degrees RMS error) on the localization test after bilateral implantation (delays: 6.8, 12, 13 and 17 years). Moreover, several studies with repeated measures showed that a second CI has no detrimental effect on performance with the first CI-only [12,21].

Litovsky et al. (2006) and Wolfe et al. (2007) reported a benefit of a second CI in prelingually deafened children on speech in noise and localization tests, even in some children who received their first CI at young age and their second CI at the age of 10-12years [19,22]. Wolfe et al. also demonstrated that children who received their second CI before the age of four, achieved better speech recognition scores for the later implanted ear than children who were implanted at later age. Wolfe et al. (2007), Gordon et al. (2009), Litovsky et al. (2006) and van Deun et al. (2010) agreed that children should receive the first implant before the age of three (Gordon et al. and van Deun et al. <2yrs) and the second one before the age of four to gain optimal auditory skill levels in each ear [6,14,19,22]. On the other hand, Galvin et al. (2008) reported a child who initially rejected the second implant that was implanted 1.2 years after the first one at the age of three [23]. They emphasized that prolonged delays might lead to disappointment and that parents should be informed that a child might not tolerate the second implant as well as their first. Galvin et al. (2008) described that for children who received both implants within a period of 2-3 years it was easier and less time-consuming to adapt to the second implant than after an extensive delay [23].

These clinical findings are supported by neurophysiological background studies that demonstrated why early implantation is essential for the success of (unilateral) cochlear implantation in prelingually deafened children. Sharma et al. (2003) investigated plasticity of the auditory system and showed that there is a critical period of three years of speech, language and auditory development [24]. Implantation after the age of three

significantly reduced the chance of success due to underdevelopment of the auditory cortex. In 2005, Sharma et al. explained the importance of early first and second implantation in children by measuring cortical auditory evoked potentials (CAEPs) and P1 cortical response latencies. They showed that implantation of both implants before the critical age of 3.5years, even with a delay between implantations, resulted in rapid development in CAEP waveform morphology and P1 latency on both sides. Late implanted children showed abnormal waveform morphology and P1 latencies. A child who received the first implant before the age of 3.5years and the second after the age of seven, had CAEP responses evoked by the second implant that were similar to late-implanted children, indicating that early implantation of the both CI's is essential for auditory cortex development [25]. Bauer et al. (2006) provided evidence that the weak ipsilateral stimulation of the auditory cortex after unilateral implantation seemed sufficient to quickly restore binaural pathways and develop the weakly stimulated cortex in two children who received their second implants five months to a year after their first. The children received both implants before the age of two years. In postlingually deafened adults, the binaural auditory system and auditory cortex are well-developed and early implantation seems less trivial [26,27].

CONCLUSION

Neurophysiological background studies provide evidence that implantation before the critical age of 3.5years of both implants is important for binaural pathway development. In postlingually deafened adults, the binaural auditory system and auditory cortex are well-developed and early second implantation seems less trivial. Current clinical evidence regarding the effect of a time delay between sequential cochlear implantations, however, suggest that a second implant can be beneficial even after a substantial delay in both postlingually deafened adults and prelingually deafened children. Nonetheless, the evidence has a significant risk of bias. High quality trials assessing the effectiveness of a second cochlear implant after a time delay should be initiated.

APPENDIX

Search query: (hearing loss OR hearing impairment OR hearing disorder OR deaf OR deafness OR complete OR acquired OR extreme OR hearing impaired OR sensory

hearing loss OR severe OR profound OR perceptive OR bilateral OR bilaterally OR cochlear implantation OR cochlear implant OR cochlear prosthesis implantation OR cochlear prosthesis implantations OR cochlear implanted OR cochlear implantee OR cochlear implantees OR cochlear implants) AND ((Sequential OR sequentially OR sequence OR delayed OR delay OR duration OR consecutive OR consecutively OR successive OR successively OR interval OR intervals OR difference OR time) AND (bilateral OR bilaterally OR binaural OR binaurally OR two-sided)) AND (cochlear implantation OR cochlear implant OR cochlear implants OR cochlear prosthesis implantation OR cochlear prosthesis implantations OR cochlear implanted OR cochlear implantee OR cochlear implantees OR cochlear implants) Field: Title/Abstract

REFERENCES

1. Papsin BC, Gordon KA. Bilateral cochlear implants should be the standard for children with bilateral sensorineural deafness. *Curr Opin Otolaryngol Head Neck Surg* 2008;16:69-74.

2. Brown KD, Balkany TJ. Benefits of bilateral cochlear implantation: a review. *Curr Opin Otolaryngol Head Neck Surg* 2007;15:315-318.

3. Murphy J, O'Donoghue G. Bilateral cochlear implantation: an evidence-based medicine evaluation. *Laryngoscope* 2007;117:1412-1418.

4. Offeciers E, Morera C, Muller J et al. International consensus on bilateral cochlear implants and bimodal stimulation. *Acta Otolaryngol* 2005;125:918-919.

5. Bond M, Mealing S, Anderson R et al. The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. *Health Technol Assess* 2009;13:1-330.

6. Gordon KA, Papsin BC. Benefits of short interimplant delays in children receiving bilateral cochlear implants. *Otol Neurotol* 2009;30:319-331.

7. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version 5.0.2 [updated September 2009].

8. Laske RD, Veraguth D, Dillier N et al. Subjective and objective results after bilateral cochlear implantation in adults. *Otol Neurotol* 2009;30:313-318.

9. Kuhn-Inacker H, Shehata-Dieler W, Muller J et al. Bilateral cochlear implants: a way to optimize auditory perception abilities in deaf children? *Int J Pediatr Otorhinolaryngol* 2004;68:1257-1266.

10. Scherf F, van DL, van WA et al. Subjective benefits of sequential bilateral cochlear implantation in young children after 18 months of implant use. *ORL J Otorhinolaryngol Relat Spec* 2009;71:112-121.

11. Steffens T, Lesinski-Schiedat A, Strutz J et al. The benefits of sequential bilateral cochlear implantation for hearing-impaired children. *Acta Otolaryngol* 2008;128:164-176.

12. Zeitler DM, Kessler MA, Terushkin V et al. Speech perception benefits of sequential bilateral cochlear implantation in children and adults: a retrospective analysis. *Otol Neurotol* 2008;29:314-325.

13. Scherf F, van Deun L, van Wieringen A et al. Hearing benefits of second-side cochlear implantation in two groups of children. *Int J Pediatr Otorhinolaryngol* 2007;71:1855-1863.

14. van Deun L, van Wieringen A, Scherf F et al. Earlier intervention leads to better sound localization in children with bilateral cochlear implants. *Audiol Neurootol* 2010;15:7-17.

15. Grieco-Calub TM, Litovsky RY. Sound Localization Skills in Children Who Use Bilateral Cochlear Implants and in Children with Normal Acoustic Hearing. *Ear Hear* 2010.

16. Nopp P, Schleich P, D'Haese P. Sound localization in bilateral users of MED-EL COMBI 40/40+ cochlear implants. *Ear Hear* 2004;25:205-214.

17. Schleich P, Nopp P, D'Haese P. Head shadow, squelch, and summation effects in bilateral users of the MED-EL COMBI 40/40+ cochlear implant. *Ear Hear* 2004;25:197-204.

18. Chang SA, Tyler RS, Dunn CC et al. Performance over time on adults with simultaneous bilateral cochlear implants. *J Am Acad Audiol* 2010;21:35-43.

19. Litovsky RY, Johnstone PM, Godar S et al. Bilateral cochlear implants in children: localization acuity measured with minimum audible angle. *Ear Hear* 2006;27:43-59.

20. Tyler RS, Dunn CC, Witt SA et al. Speech perception and localization with adults with bilateral sequential cochlear implants. *Ear Hear* 2007;28:86S-90S.

21. Ramsden R, Greenham P, O'Driscoll M et al. Evaluation of bilaterally implanted adult subjects with the nucleus 24 cochlear implant system. *Otol Neurotol* 2005;26:988-998.

22. Wolfe J, Baker S, Caraway T et al. 1-year postactivation results for sequentially implanted bilateral cochlear implant users. *Otol Neurotol* 2007;28:589-596.

23. Galvin KL, Mok M, Dowell RC et al. Speech detection and localization results and clinical outcomes for children receiving sequential bilateral cochlear implants before four years of age. *Int J Audiol* 2008;47:636-646.

24. Sharma A, Dorman MF, Spahr AJ. A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear Hear* 2002;23:532-539.

25. Sharma A, Dorman MF, Kral A. The influence of a sensitive period on central auditory development in children with unilateral and bilateral cochlear implants. *Hearing Research* 2005;203:134-143

26. Bauer PW, Sharma A, Martin K et al. Central auditory development in children with bilateral cochlear implants. *Arch Otolaryngol Head Neck Surg* 2006;132:1133-1136.

27. Eggermont JJ. The role of sound in adult and developmental auditory cortical plasticity. *Ear Hear* 2008;29:819-829.

CHAPTER 07

Discussion

As we outlined in the introduction of this thesis, bilateral cochlear implantation (BiCI) is not reimbursed by insurance companies in adults and children above the age of 5 years, unless deafness is caused by meningitis. The reason for this is that there is a lack of well-performed studies with little chance of bias that demonstrate the benefits of BiCI compared to unilateral cochlear implantation (UCI) [1,2].

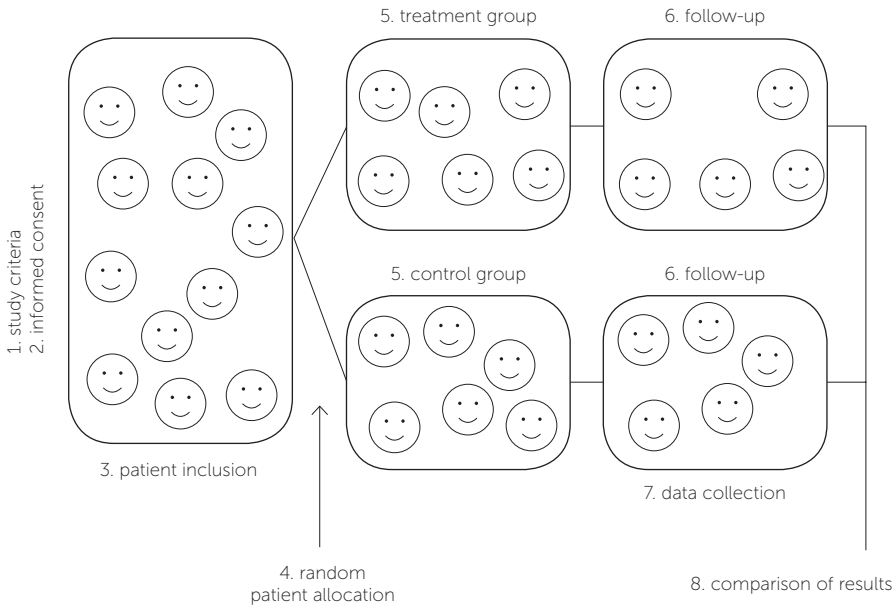
7.1 Bias

Bias means systematic favoritism that leads to misleading results [3]. Bias can occur during the participants' selection process, experiments, data collection, statistical analyses and reporting of results. An example of selection bias is the following: if you would want to estimate how much beer an average Dutch man drinks in a month, and you would ask all 20,000 men leaving a soccer stadium on a Sunday afternoon, the result of your sample will probably be higher than if you would ask 20,000 men leaving a Céline Dion concert. There are many other types of bias, like allocation bias: when certain participants are allocated to one study group and certain participants to another, exclusion bias: when certain individuals are systematically excluded from the study altogether, attrition bias: when patients are lost to follow-up without an explanation, or when the loss to follow-up is not reported or taken into account in the statistical analyses, recall bias: when participants are not able to accurately recall information from the past, observer bias: when a researcher (unconsciously) influences the experiment by the way the experiment is carried out or the data written down, or reporting bias: when researchers selectively report some results and leave other results out [4].

7.2 Randomized controlled trial (RCT)

An RCT is considered the gold standard for clinical trials. It is a type of study in which participants are randomly allocated to different treatment groups (or a treatment group and placebo group). The independently performed allocation process takes place after the study eligibility criteria have been checked and after the participants have given their consent to participate. When randomization and treatment have taken place, the participants all undergo the same tests during the follow-up period. In this manner, the only difference between the groups is the treatment they receive (cf. Figure 1). The major advantage of this type of research is the prevention of allocation bias. Without randomization, care givers or researchers can (unconsciously) influence the allocation process and the results can be influenced by known or unknown prognostic factors.

Figure 1 | A Randomized Controlled Trial



A disadvantage and reason why RCTs are not as frequently performed as desired, is that designing and executing an RCT is time-consuming and thereby costly. Furthermore, in certain situations, randomization can be unethical if it is known that one treatment is superior to the other. For this latter reason, an RCT to investigate the benefits of BiCI compared to UCI in children has never taken place.

Besides allocation bias, exclusion bias is prevented when using an RCT. An observer bias can be prevented by blinding the researchers, although this is not always possible. For example, in our study, one could see on the outside if a patient had been implanted unilaterally or bilaterally. In order to prevent reporting bias, most journals only accept a manuscript if the trial had been registered in a trial register at the beginning of the study. It is also common nowadays, to publish a study protocol at the beginning of a study.

7.3 Levels of evidence and the value of a Randomized Controlled Trial (RCT)

When reviewing literature, the quality of reports is usually systematically assessed. A study can be given a Level of Evidence (LoE), based on the inherent strength of the design (cf. Table 1) [5].

Table 1| Level of evidence

Level of evidence	
Ia	Evidence for meta-analysis of randomised controlled trials
Ib	Evidence from at least one randomised controlled trial
Iia	Evidence from at lease one controlled study without randomisation
Iib	Evidence from at lease one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

The majority of the studies published on the potential benefits of BiCI versus UCI are level III studies. They are predominantly non-randomized cross-sectional or cohort studies, comparing a group of unilaterally implanted subjects with a group of bilaterally implanted subjects [6-8]. Other studies compared two matched study groups [9], or compared pre- and postoperative results after sequential implantation, in a group of patients who had already been implanted unilaterally [10]. Furthermore, there are studies in which a cohort of bilateral implantees was asked to de-activate one implant to assess the differences between unilateral and bilateral hearing [11-13]. This is however, not representative for actual UCI, as these patients had been used to listening with two implants in daily life. Also, implantation may have caused insertion damage to the cochlea, deteriorating residual hearing [14].

There are ample prospective studies on UCI versus BiCI, with well-described study eligibility criteria. Yet, in the majority of these studies, the participants had not been randomly allocated to the treatment groups or missing data, loss to follow-up and confounding factors had not been taken into account [14].

7.4 Contribution of this thesis to the current knowledge

In this thesis, we have shown the results of the first RCT on BiCI compared to UCI in postlingually deafened adults. Our hypothesis was that BiCI would be beneficial over UCI. Unlike in children, it was ethical to allocate participants to either unilateral or bilateral implantation, because UCI is still the standard treatment. Participation in this study gave patients an opportunity to receive a non-conventional (and presumably better) treatment. With this RCT, we found that BiCI did not only give deaf patients the ability to hear significantly better in difficult listening situations, but the subjective benefits also outweighed the costs.

7.5 Cost-Utility Analysis

A euro, dollar, pound or yen can only be spent once. Based on the wealth and culture of a country, policy makers decide which treatments are paid for with public money and which not. Each country has its own generally accepted "willingness-to-pay (WTP) threshold". The WTP indicates how much people are willing to spend on one additional life year in good health (quality-adjusted life year or QALY). In North America, this threshold is about $50,000/QALY and in the UK, £20,000-£30,000. In the Netherlands, the WTP varies between €24,500 and €80,000, dependent on the seriousness of the disease [15-17].

Cost-utility (or cost-effectiveness) analyses are important tools for health care policy makers. The result of a cost-utility analysis is an ICUR, an "incremental cost-utility ratio". An ICUR represents the ratio of incremental costs per QALY gained. (ICUR = (costs of treatment X - costs of treatment Y) / (utility of treatment X – utility of treatment Y (in QALYs)). Typically, an intervention is considered cost-effective if the ICUR falls below the WTP-threshold.

Cost-utility analyses are complex, because they are dependent on many different factors. Costs can be estimated from the perspective of a society, patient, Ministry of Health, or health insurance company [18].

We decided to perform cost utility analyses from a health insurance perspective and showed that simultaneous BiCI is cost-effective if the implants are used for at least 5-10 years, based on universally applied quality of life and quality of hearing questionnaires.

7.6 Future Studies

7.6.1 Future studies on cost-utility

In future studies, it would be interesting to perform cost-utility analyses from a societal perspective. In such analyses, not only direct health care costs (like hospitalization, surgery, medication) and direct non-healthcare costs (travel expenses) should be included, but also indirect non-healthcare costs. Productivity loss (of paid and unpaid work) is an example of indirect non-healthcare costs [18].

7.6.2 Future studies on sequential cochlear implantation

If BiCI will become a standard treatment, many unilaterally implanted subjects will be interested in receiving a second implant. In order to investigate how much benefit patients will gain from sequential BiCI, further research can be necessary.

Fayad and Linthicum (2006) showed that spiral ganglion cells (SGCs) in the auditory nerve degenerate after sensory neural hearing loss [19]. SGCs have an important role in cochlear implantation. Cochlear implants convert sounds into electrical pulses that are transferred to the spiral ganglion cells (SGCs) [20]. Seyyedi et al. (2014) demonstrated that word recognition is positively correlated to SGC count [21]. Although it is not well known how long it takes before the cochlear nerve can no longer be stimulated, minimization of the inter-implantation period seems preferable. In chapter 6 we reviewed the literature on time between sequential cochlear implantations. We demonstrated that a second implant may be beneficial in postlingually deafened adults, even after years of unilateral use. Laske et al. (2009) even reported subjective benefits of BiCI after 19 years of unilateral implantation [11]. However, since all articles had a level of evidence of III, prospective studies are needed to investigate the effect of time between sequential cochlear implantations.

The unilaterally implanted patients studied in this thesis, received a second cochlear implant after two years of unilateral use. Objective and subjective hearing tests will be performed one and two years after sequential bilateral implantation. These results can be compared with the patients' preoperative results and with the results of the simultaneously implanted bilateral implantees. This will give us an idea of the effect of a two-year gap between sequential implantations.

As soon as bilateral implantation will be more broadly applied, prospective studies can be performed to investigate additional effects of time between sequential implantations.

7.7 Eligibility criteria

The eligibility criteria for CI have changed continuously in the past thirty years. Nowadays, patients are provided with implants at younger age (even at the age of 6 months) and with less severe hearing loss than in the earlier days. This thesis provides evidence for even further widening of the eligibility criteria. It shows that BiCI should be a standard treatment for postlingually deafened adult patients.

REFERENCES

1. van Schoonhoven J, Sparreboom M, van Zanten GA, Scholten RJPM, Mylanus EAM, Grolman W, Maat A. The Effectiveness of Bilateral Cochlear Implants for Severe to Profound Deafness in Children and Adults. A systematic review. *CI-ON* 2009. Report commissioned by: CVZ On behalf of: CI-ON.

2. Schoonhoven van J, Sparreboom M, Zanten van GA et al. The Effectiveness of Bilateral Cochlear Implants for Severe-to-Profound Deafness in Adults: A Systematic Review. *Otol Neurotol* 2013;34(2):190-8.

3. Rumsey DJ. Statistics For Dummies, 2nd Edition: Wiley Publishing Inc.; 2011. How to Identify Statistical bias.

4. Rothman, K.J. *Modern Epidemiology.* Lippincott Williams & Wilkins; 2008. pp.134-137.

5. Shekelle PG, Woolf WH, Eccles M, Grimshaw J. Clinical guidelines: Developing guidelines. *BMJ* 1999;318:593–6.

6. Noble W, Tyler R, Dunn C, Bhullar N. Unilateral and bilateral cochlear implants and the implant-plus-hearing-aid profile: comparing self-assessed and measured abilities. *Int J Audiol* 2008b;47:505-14.

7. Zeitler DM, Kessler MA, Terushkin V et al. Speech perception benefits of sequential bilateral cochlear implantation in children and adults: a retrospective analysis. *Otol Neurotol* 2008;29:314-325.

8. Noble W, Tyler RS, Dunn CC, Bhullar N. Younger- and Older-Age Adults With Unilateral and Bilateral Cochlear Implants: Speech and Spatial Hearing Self-Ratings and Performance. *Otol Neurotol* 2009;30:921-9.

9. Dunn CC, Noble W, Tyler RS, Kordus M, Gantz BJ, Ji H. Bilateral and Unilateral Cochlear Implant Users Compared on Speech Perception in Noise. *Ear Hear* 2010;31:296-8.

10. Summerfield AQ, Barton GR, Terushkin V, et al. Self reported benefits from successive bilateral cochlear implantation in post-lingually deafened adults: Randomized controlled trial. *Int J Audiol* 2006;45:S99-107.

11. Laske RD, Veraguth D, Dillier N, et al. Subjective and objective results after bilateral cochlear implantation in adults. *Otol Neurotol* 2009;30:313–318.

12. Litovsky R, Parkinson A, Arcaroli J, Sammeth C. Simultaneous bilateral cochlear implantation in adults: a multicenter clinical study. *Ear Hear* 2006;27:714-31.

13. Buss E, Pillsbury HC, Buchman CA, et al. Multicenter U.S. bilateral MED-EL cochlear implantation study: speech perception over the first year of use. *Ear Hear* 2008;29(1):20-32.

14. Crathorne L, Bond M, Cooper C et al. A systematic review of the effectiveness and cost-effectiveness of bilateral multichannel cochlear implants in adults with severe-to-profound hearing loss. *Clin Otolaryngol* 2012;37:342–54.

15. Shiroiwa T, Igarashi A, Fukuda T, Ikeda S. WTP for a QALY and health states: More money for severer health states? *Cost Effectiveness and Resource Allocation* 2013; 11:22.

16. van Gils PF, Schoemaker CG, Polder JJ. Stand van zaken. Hoeveel mag een gewonnen levensjaar kosten? Onderzoek naar de waardering van de QALY. *Ned Tijdschr Geneeskd* 2013; 157: A6507.

17. Bobinac A, Van Exel NJ, Rutten FF, Brouwer WB. Willingness to pay for a quality-adjusted life-year: the individual perspective. *Value Health* 2010; 13(8):1046-55.

18. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg. College voor zorgverzekeringen, 2011; Geactualiseerde versie 2010.

19. Fayad JN, Linthicum Jr. FH. Multichannel cochlear implants: relation of histopathology to performance. *Laryngoscope* 2006;116:1310-1320.

20. Ramekers D, Versnel H, Strahl SB, Klis SFL, Grolman W. Recovery characteristics of the electrically stimulated auditory nerve in deafened guinea pigs: Relation to neuronal status. *Hearing Research* 2015;321:12-24.

21. Seyyedi, M, Viana, LM, Nadol Jr., JB. Within-subject comparison of word recognition and spiral ganglion cell count in bilateral cochlear implant recipients. *Otol Neurotol* 2014;35:1446-1450.

Summary | Samenvatting

SUMMARY

Chapter 1 gives a description of the physiology of normal hearing and hearing loss. It defines the effects that are used for binaural hearing: head shadow, squelch, summation, inter aural time difference (ITD) and inter aural level difference (ILD). Furthermore, the eligibility criteria for hearing aid use and cochlear implantation (CI) are discussed. This chapter also describes the impact of hearing loss on our society and why, currently, Dutch insurance companies reimburse only one cochlear implant in adults. It explains that there is a lack of well-designed studies that demonstrate the benefits and cost-benefits of bilateral CI (BiCI) compared to unilateral CI (UCI). This is why we performed a randomized controlled trial (RCT) to compare BiCI to UCI in postlingually deafened adults.

In **Chapter 2**, we describe the Advanced Bionics ® (AB)-York crescent of sound. This is a new test setup that comprises speech intelligibility in noise and localization tests that represent everyday listening situations. One of its tests is the Sentence Test with Adaptive Randomized Roving levels (STARR) with sentences and noise both presented from straight ahead. For the Dutch population, we adopted the AB- York setup and replaced the English sentences with a validated set of Dutch sentences. The Dutch version of the STARR is called the Utrecht-STARR (U-STARR). In this chapter, the validity and reliability of the U-STARR are described and the test is compared to the former Dutch gold standard for speech-in-noise testing; the Plomp test. It shows that the U-STARR is adequate and reliable and seems better suited for severely hearing-impaired persons than the conventional Plomp test.

Chapter 3 shows the first important outcomes of the RCT, comparing the effects of UCI versus BiCI in 38 adults. Nineteen patients received one cochlear implant (and, if desired, a contralateral hearing aid) and 19 patients received 2 cochlear implants simultaneously. The primary outcome was the U-STARR. Secondary outcomes were CVC words in silence, SISSS (speech-intelligibility test with spatially separated sources), sound localization and quality of hearing questionnaires. The groups were equal at baseline. At 1–year follow-up, there were no significant differences between groups on the U-STARR or CVC test. The BiCI group performed significantly better than the UCI group when signal and noise came from different directions and they were able

to localize sounds (which the UCI group was not). These results were consistent with the patients' self-reported hearing capabilities. This chapter demonstrates that there is a significant benefit of simultaneous BiCI above UCI in daily listening situations for postlingually deafened adults.

In **Chapter 4**, the cost-utility of simultaneous BiCI and UCI are analyzed and compared, using the results of the same RCT. Health utility was assessed with the Health Utilities Index 3 (HUI3), Time Trade-Off (TTO), Visual Analogue Scale (VAS) on hearing, VAS on general health and EuroQol-5D (EQ-5D). We modeled the incremental cost per quality-adjusted life year (QALY) of UCI versus BiCI over periods of 2, 5, 10, 25 years, and actual life-expectancy. The initial direct costs for UCI and BiCI were €43,883 and €87,765 respectively. Annual costs from the second year onward were €3,435 and €6,871 respectively. A cost-utility analysis revealed that a second implant became cost-effective after a 5-10-year period, based on the HUI3, TTO and VAS on hearing. This chapter shows that, compared to Dutch accepted societal willingness-to-pay thresholds, simultaneous BiCI is a cost-effective treatment for patients with a life expectancy of 5-10 years or longer.

Chapter 5 analyzes correlations between subjective and objective results on sound perception and localization tests, in the BiCI and UCI group. We calculated correlations between the Speech, Spatial and Qualities Hearing Scale (SSQ) and Nijmegen Cochlear Implant Questionnaire (NCIQ) on the one hand, and objectively measured speech perception and localization skills on the other hand. Although we found several significant correlations between the subjective and objective tests, this was particularly the case in bilaterally implanted CI users. This chapter describes the discrepancies in correlations between unilaterally and bilaterally implanted patients and why the two tests cannot substitute each other, but should both be carried out for proper evaluation of CI.

Chapter 6 investigates the effect of time between sequential CIs on hearing results in both adults and children, using a systematic review of cohort studies. Eleven studies were included. Although the quality of studies was poor, due to significant risks of bias, all studies reported that auditory performance was better in a bilateral listening situation than with either one cochlear implant activated alone. Five studies discussed

postlingually deafened adults. In four, bilateral hearing was not affected by the length of the interval between implantations. One study did report a negative effect of interval length on speech intelligibility in silence. Seven studies discussed prelingually deafened children. None reported a negative effect of the interval length on sound localization performance. One study reported poorer results after extended intervals on speech intelligibility in silence and two in noise. **Chapter 6** shows that a second implant can be beneficial even with a substantial interval between implantations, although the quality of the evidence was rather poor.

Chapter 7 is a discussion of the preceding chapters of this thesis. As we explained earlier, the lack of well-designed, well-executed studies formed the basis of this thesis and the reason why we designed an RCT. This chapter describes several kinds of bias and shows how valuable an RCT is, since this study design prevents several kinds of bias.

As usual, when one tries to find answers to certain research questions, other questions rise. This chapter gives suggestions for research questions that can be answered in future studies.

SAMENVATTING

Hoofdstuk 1 beschrijft de werking van een normaal gehoor en van gehoorverlies. Het definieert de effecten die gebruikt worden bij binauraal horen (horen met twee oren): hoofdschaduw, squelch, summatie, inter aural time difference (ITD) en inter aural level difference (ILD). Ook wordt uitgelegd wanneer iemand in aanmerking komt voor een hoortoestel of voor cochleaire implantatie (CI). In dit hoofdstuk wordt de impact van gehoorverlies op onze maatschappij beschreven en waarom Nederlandse zorgverzekeringen momenteel in de meeste gevallen slechts één cochleair implantaat vergoeden. Dit hoofdstuk laat zien dat er een tekort is aan kwalitatief goede studies die onderzoek doen naar de effectiviteit en kosten-effectiviteit van bilaterale CI (BiCI) vergeleken met unilaterale CI (UCI). Wij hebben een gerandomiseerd, gecontroleerd onderzoek (een randomized controlled trial (RCT)) uitgevoerd om BiCI te vergelijken met UCI in postlinguaal dove volwassenen.

In **hoofdstuk 2** beschrijven we de Advanced Bionics ® (AB)-York crescent of sound. Dit is een nieuwe testopstelling waarmee spraak-in-ruis testen en lokalisatie testen kunnen worden uitgevoerd. Dit zijn situaties, zoals die in het dagelijks leven voorkomen. Eén van de testen is de Sentence Test with Adaptive Randomized Roving levels (STARR), waarbij zinnen en ruis beiden recht van voren worden aangeboden. Voor de Nederlandse populatie hebben we de Engelse zinnen in de AB-York opstelling vervangen door een gevalideerde set Nederlandse zinnen. De Nederlandse versie van de STARR wordt de Utrecht-STARR (U-STARR) genoemd. In dit hoofdstuk worden de validiteit en betrouwbaarheid van de U-STARR beschreven en de test wordt vergeleken met de voorgaande Nederlandse gouden standaard voor het testen van spraak in ruis: de Plomp test. Dit hoofdstuk laat zien dat de U-STARR een betrouwbare test is en beter geschikt voor ernstig slechthorenden dan de conventionele Plomp test.

Hoofdstuk 3 geeft de eerste resultaten weer van de RCT waarin UCI vergeleken wordt met BiCI bij 38 volwassenen. Negentien patiënten ontvingen één cochleair implantaat (en gebruikten eventueel een contralateraal hoortoestel) en 19 patiënten ontvingen twee cochleair implantaten tijdens één operatie. De primaire uitkomstmaat was de U-STARR. Secundaire uitkomstmaten waren CVC woorden in stilte, de SISSS (spraak in ruis van verschillende richtingen), lokalisatie van geluiden en vragenlijsten over kwaliteit

van horen. De groepen waren vergelijkbaar aan het begin van de studie. Na 1 jaar werden er geen verschillen gemeten tussen de groepen met de U-STARR of CVC test. Wel presteerde de BiCI groep significant beter dan de UCI groep wanneer signaal en ruis van verschillende richtingen kwamen. Ook was de BiCI groep in staat geluiden te lokaliseren, iets waartoe de UCI groep niet in staat was. Deze resultaten kwamen overeen met de zelf-gerapporteerde uitkomsten op de vragenlijsten. Dit hoofdstuk laat zien dat BiCI significante voordelen heeft boven UCI in dagelijkse luistersituaties voor postlinguaal dove volwassenen.

In **hoofdstuk 4** worden de kosten-utiliteit van BiCI en UCI geanalyseerd en met elkaar vergeleken. Hierbij werden de resultaten gebruikt van de eerder beschreven RCT. Health utility (gezondheidsutiliteit) werd gemeten met de Health Utilities Index 3 (HUI3), Time Trade-Off (TTO), een Visual Analogue Scale (VAS) over het gehoor, een VAS over algemene gezondheid en de EuroQol-5D (EQ-5D). We hebben de toename in kosten per quality-adjusted life year (QALY) van UCI en BiCI berekend voor veronderstelde periodes van 2, 5, 10, 25 jaar en de eigenlijke levensverwachting per patiënt. De initiële directe kosten voor UCI en BiCI bedroegen resp. €43,883 en €87,765. De jaarlijkse kosten die gemaakt werden vanaf het jaar na implantatie bedroegen resp. €3,435 en €6,871. De kosten-utiliteits-analyses lieten zien dat een tweede CI kosteneffectief werd na 5-10jaar, gebaseerd op uitkomsten van de HUI3, TTO en VAS over het gehoor. Dit hoofdstuk laat zien dat, vergeleken met de willingness-to-pay (WTP) drempels in Nederland, simultane BiCI kosteneffectief is wanneer een patiënt een levensverwachting heeft van ten minste 5-10 jaar.

In **hoofdstuk 5** worden correlaties berekend tussen objectieve en subjectieve uitkomsten van testen van het gehoor en lokalisatie van geluiden, voor zowel de UCI als BiCI groep. We hebben de correlaties berekend tussen de Speech, Spatial and Qualities Hearing Scale (SSQ) en Nijmegen Cochlear Implant Questionnaire (NCIQ) aan de ene kant en objectief gemeten spraak-verstaan en lokalisatietesten aan de andere kant. Hoewel we significante correlaties vonden tussen de subjectieve en objectieve uitkomsten, was dit met name het geval voor de BiCI groep. Dit hoofdstuk beschrijft de discrepanties in correlaties tussen de UCI en BiCI groep en laat zien waarom de twee testen elkaar niet kunnen vervangen, maar beiden toegepast dienen te worden bij gedegen evaluatie van CI.

In **hoofdstuk 6** wordt onderzocht wat het effect van een tijdsinterval is tussen opeenvolgende implantaties, op hoor-resultaten bij zowel volwassenen als kinderen. Hiervoor hebben we een systematische review van cohort studies uitgevoerd. Elf studies werden geïncludeerd. Hoewel de kwaliteit van de studies matig was door significante risico's op bias, lieten alle studies zien dat patiënten beter presteerden met twee cochleair implantaten dan met één. Vijf studies gingen over postlinguaal dove volwassenen. In vier van deze studies leek het presteren met twee cochleair implantaten niet beïnvloed te zijn door de lengte van het interval tussen de opeenvolgende implantaties. Eén studie liet een negatief effect zien van een lang tijdsinterval tussen implantaties op spraak-verstaan resultaten in stilte. Zeven studies gingen over prelinguaal dove kinderen. Geen van deze studies rapporteerden een negatief effect van de lengte van het tijdsinterval op geluidslokalisatieprestaties. Eén studie beschreef slechtere resultaten op spraak-verstaan-testen in stilte en twee studies in ruis, bij een lang tijdsinterval. Hoofdstuk 6 laat zien dat een tweede implantaat voordelen geeft, ook wanneer deze lang na het eerste cochleair implantaat geplaatst wordt, hoewel de kwaliteit van de studies matig was.

Hoofdstuk 7 is een discussie van de voorgaande hoofdstukken van dit proefschrift. Zoals we eerder beschreven, vormde het gebrek aan kwalitatief goede studies de basis voor deze promotie. Om deze reden hebben we een RCT ontworpen en uitgevoerd. Dit hoofdstuk beschrijft verschillende soorten bias en laat zien hoe waardevol een RCT is, omdat met dit studieontwerp een aantal soorten bias voorkomen wordt. Zoals gebruikelijk, levert het beantwoorden van onderzoeksvragen weer nieuwe vragen op. In dit hoofdstuk worden suggesties gegeven voor onderzoeksvragen voor toekomstige studies.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DANKWOORD

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List of publications

LIST OF PUBLICATIONS

1. Iwasaki S, **Smulders YE**, Burgess AM, McGarvie LA, Macdougall HG, Halmagyi GM, Curthoys IS. Ocular Vestibular Evoked Myogenic Potentials in Response to Bone-Conducted Vibration of the Midline Forehead at Fz. A New Indicator of Unilateral Otolithic Loss. *Audiol Neurootol.* 2008;13(6):396-404.

2. Iwasaki S, **Smulders YE**, Burgess AM, McGarvie LA, Macdougall HG, Halmagyi GM, Curthoys IS. Ocular vestibular evoked myogenic potentials to bone conducted vibration of the midline forehead at Fz in healthy subjects. *Clin Neurophysiol*. 2008;119(9):2135-47.

3. Iwasaki S, Chihara Y, **Smulders YE**, Burgess AM, Halmagyi GM, Curthoys IS, Murofushi T. The role of the utricular macula and the superior vestibular nerve in the generation of ocular vestibular-evoked myogenic potentials to bone conducted vibration at Fz. *Clin Neurophysiol*. 2009 Mar;120(3):588-93.

4. **Smulders YE**, Welgampola MS, Burgess AM, McGarvie LA, Halmagyi GM, Curthoys IS. The n10 component of the ocular vestibular evoked myogenic potential (oVEMP) is distinct from the R1 component of the blink reflex. *Clin Neurophysiol*. 2009 Aug;120(8):1567-76.

5. Curthoys IS, Burgess AM, MacDougall HG, McGarvie LA, Halmagyi GM, **Smulders YE**, Iwasaki S. Testing Human Otolithic Function Using Bone-conducted Vibration. *Ann N Y Acad Sci*. 2009 May;1164:344-6

6. Curthoys IS, Manzari L, **Smulders YE**, Burgess AM. A review of the scientific basis and practical application of a new test of utricular function – ocular vestibular – evoked myogenic potentials to bone-conducted vibration. *ACTA otorhinolaryngologica italica* 2009;29:179-186

7. **Smulders YE**, de Bondt RBJ, Lacko M, Hodge JAL, Kross KW. Laryngeal tuberculosis presenting as supraglottic carcinoma: A case report and review of the literature. *Journal of Medical Case Reports* 2009, 3:9288

8. Tange RA, **Smulders YE**, Grolman W. Our Experience with Bilateral Cochlear Implantations Using a Suprameatal Approach. *Int. Adv. Otol*. 2011;7(1):31-34.

9. **Smulders YE**, Rinia AB, Rovers MM, van Zanten GA, Grolman W. What is the effect of time between sequential cochlear implantations on hearing in adults and children? A systematic review of the literature. *Laryngoscope*. 2011;121(9):1942-9.

10. Lammers MJ, Grolman W, **Smulders YE**, Rovers MM. The cost-utility of bilateral cochlear implantation: a systematic review. *Laryngoscope*. 2011;121(12):2604-9.

11. **Smulders YE**, Rinia AB, Pourier VEC, Van Zon A, Van Zanten GA, Stegeman I, Scherf FWAC, Smit AL, Topsakal V, Tange RA, Grolman W. Validation of the U-STARR with the AB-York Crescent of Sound, a New Instrument to Evaluate Speech Intelligibility in Noise and Spatial Hearing Skills. *Audiol Neurotol Extra* 2015;5:1-10.

12. Van Zon A, **Smulders YE**, Ramakers GGJ, Stegeman I, Smit AL, Van Zanten GA, Stokroos RJ, Hendrice N, Free RH, Bert Maat B, Frijns JHM, Mylanus EAM, Huinck WJ, Topsakal V, Tange RA, Grolman W. The effect of unilateral and simultaneous bilateral cochlear implantation on tinnitus; a prospective study. *Laryngoscope*. 2015 Aug 8.

13. **Smulders YE**, Van Zon A, Stegeman I, Rinia AB, Van Zanten GA, Stokroos RJ, Hendrice N, Free RH, Maat B, Frijns JHM, Mylanus EAM, Huinck WJ, Topsakal V, Grolman W. Cost–utility of bilateral versus unilateral cochlear implantation in adults; a randomized controlled trial. *Otol Neurotol* 2016;37(1):38-45

14. **Smulders YE**, van Zon A, Stegeman I, Rinia AB, Van Zanten GA, Stokroos RJ, Hendrice N, Free RH, Maat B, Frijns JHM, Briaire JJ, Mylanus EAM, Huinck WJ, Smit AL, Topsakal V, Tange RA, Grolman W. A randomized controlled trial showing a higher benefit of bilateral over unilateral cochlear implantation in adult patients. *Accepted in JAMA Otolaryngol Head Neck Surg.*

About the author

CURRICULUM VITAE

Yvette Evelien Smulders was born on 21 September 1981 in Helmond, the Netherlands. She graduated from the Dr. Knippenbergcollege in 1999 and became a student at Maastricht University where she studied Health Sciences and Medicine. She was a member of the 'Saurus Rowing Association' and 'Student Association Tragos'. Furthermore, she was a member of the University's student council for several years. In her final year of medical school, she spent six months at the otolaryngology, head and neck department of the Maastricht University Medical Center, supervised by Prof. Dr. R.J. Stokroos. She graduated from medical school in 2007 and became a research fellow at Sydney University, Australia and the Massachusetts Eye and Ear Infirmary in Boston, USA, where she worked on the development of a new vestibular test: the OVEMP. After spending a year and a half abroad, she returned to the Netherlands. In 2009, she started her Ph.D project at the otolaryngology, head and neck department of the University Medical Center Utrecht. Her Ph.D, that led to this thesis, was supervised by Prof. Dr. W. Grolman and Dr. G.A. Van Zanten. Yvette was a resident in otolaryngology, head and neck surgery, from 2010 up until 2015. During this residency, she also worked at the St. Antonius Hospital, Nieuwegein (supervised by Dr. M. Copper), Gelderse Vallei Hospital, Ede (supervised by Dr. M.H.J.M. Majoor) and Deventer Ziekenhuis (supervised by Dr. J. Buwalda).