



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2013

**Factors Affecting Auditory Performance of Postlinguistically Deaf Adults Using
Cochlear Implants: An Update with 2251 Patients**

Blamey, P ; Artieres, F ; et al

DOI: <https://doi.org/10.1159/000343189>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-69118>

Journal Article

Accepted Version

Originally published at:

Blamey, P; Artieres, F; et al (2013). Factors Affecting Auditory Performance of Postlinguistically Deaf Adults Using Cochlear Implants: An Update with 2251 Patients. *Audiology and Neurotology*, 18(1):36-47.

DOI: <https://doi.org/10.1159/000343189>

Factors Affecting Auditory Performance of Postlinguistically Deaf Adults Using Cochlear Implants: An Update with 2251 Patients

Peter Blamey^{a,c} Françoise Artieres^{d,e} Deniz Başkent^{j,k} François Bergeron^m Andy Beynon^l
Elaine Burkeⁿ Norbert Dillier^p Richard Dowell^c Bernard Fraysse^f Stéphane Gallégo^g
Paul J. Govaerts^q Kevin Green^o Alexander M. Huber^p Andrea Kleine-Punte^r Bert Maat^j
Mathieu Marx^f Deborah Mawman^o Isabelle Mosnier^h Alec Fitzgerald O'Connorⁿ
Stephen O'Leary^b Alexandra Rousset^c Karen Schauwers^q Henryk Skarzynski^s
Piotr H. Skarzynski^{s,t} Olivier Sterkers^h Assia Terrantiⁱ Eric Truy^g Paul Van de Heyning^r
Frédéric Venail^e Christophe Vincentⁱ Diane S. Lazard^a

^aBionics Institute, and Departments of ^bOtolaryngology, and ^cAudiology and Speech Pathology, The University of Melbourne Cochlear Implant Clinic, The Royal Victorian Eye and Ear Hospital, Melbourne, Vic., Australia; ^dService d'Audiophonologie et ORL, Institut Saint-Pierre, Palavas-les-Flots, ^eService d'ORL et Chirurgie Cervico-Faciale, CHU Gui-de-Chauliac, Montpellier, ^fService d'ORL et Chirurgie Cervico-Faciale, Hôpital Universitaire Purpan, Toulouse, ^gDépartement d'ORL, de Chirurgie Cervico-Maxillo-Faciale et d'Audiophonologie, Hôpital Edouard-Herriot, Hospices Civils de Lyon, Lyon, ^hService d'ORL et Chirurgie Cervico-Faciale, AP-HP, Hôpital Beaujon, Clichy, and ⁱService d'otologie et d'otoneurologie, Hôpital R.-Salengro, CHRU de Lille, Lille, France; ^jDepartment of Otorhinolaryngology/Head and Neck Surgery, Cochlear Implant Center Northern Netherlands, University Medical Center Groningen, University of Groningen, and ^kGraduate School of Medical Sciences, Research School of Behavioural and Cognitive Neurosciences, University of Groningen, Groningen, and ^lDepartment of Otorhinolaryngology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; ^mFaculté de médecine, Université Laval, Québec, Qué., Canada; ⁿAuditory Implants Department, St Thomas' Hospital, London, and ^oUniversity of Manchester, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK; ^pDepartment of Otorhinolaryngology, University Hospital of Zurich, Zurich, Switzerland; ^qThe Eargroup, and ^rUniversity Department of Otorhinolaryngology and Head and Neck Surgery, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium; ^sInstitute of Physiology and Pathology of Hearing, Warsaw, and ^tInstitute of Sensory Organs, Kajetany, Poland

© Free Author Copy – for personal use only

ANY DISTRIBUTION OF THIS ARTICLE WITHOUT WRITTEN CONSENT FROM S. KARGER AG, BASEL IS A VIOLATION OF THE COPYRIGHT.

Written permission to distribute the PDF will be granted against payment of a permission fee, which is based on the number of accesses required. Please contact permission@karger.ch

Key Words

Cochlear implant · Percentile rank · Hearing loss · Plasticity · General linear model · Learning curve

Abstract

Objective: To update a 15-year-old study of 800 postlinguistically deaf adult patients showing how duration of severe to profound hearing loss, age at cochlear implantation (CI), age at onset of severe to profound hearing loss, etiology and CI

experience affected CI outcome. **Study Design:** Retrospective multicenter study. **Methods:** Data from 2251 adult patients implanted since 2003 in 15 international centers were collected and speech scores in quiet were converted to percentile ranks to remove differences between centers. **Results:** The negative effect of long duration of severe to pro-

The authors are listed in alphabetical order, except for the first and last authors.

found hearing loss was less important in the new data than in 1996; the effects of age at CI and age at onset of severe to profound hearing loss were delayed until older ages; etiology had a smaller effect, and the effect of CI experience was greater with a steeper learning curve. Patients with longer durations of severe to profound hearing loss were less likely to improve with CI experience than patients with shorter duration of severe to profound hearing loss. **Conclusions:** The factors that were relevant in 1996 were still relevant in 2011, although their relative importance had changed. Relaxed patient selection criteria, improved clinical management of hearing loss, modifications of surgical practice, and improved devices may explain the differences.

Copyright © 2012 S. Karger AG, Basel

Introduction

The outcome measures for adult recipients of cochlear implants (CIs) vary over a wide range, and it is of scientific and clinical relevance to understand the factors underlying this variability. In 1996, a retrospective analysis of speech recognition in quiet for 808 postlinguistically deafened adults using CIs described clinical predictors that accounted for 21% of the variance in CI performance [Blamey et al., 1996]. This is still the largest study that has been published, although there are numerous other papers that have considered smaller datasets and generally concentrated on a few factors [Cullen et al., 2004; Durisin et al., 2010; Finley et al., 2008; Green et al., 2007; Mack et al., 2006; Matterson et al., 2007; Rubinstein et al., 1999; Yukawa et al., 2004].

The factor accounting for the largest proportion of the variance in the 1996 study was duration of deafness, defined as the time between the onset of profound hearing loss [pure-tone hearing threshold average (PTA) ≥ 90 dB HL] and the date of implantation. Longer duration of deafness negatively influenced the outcomes. Two factors, linked to the duration of deafness, age at onset of deafness and age at implantation, were also negatively correlated with the outcomes. Within the etiologies, bacterial labyrinthitis resulted in poorer outcomes than the average for all etiologies and Ménière's disease resulted in better than average outcomes. The duration of implant experience played a positive role yielding increasing performance up to 3 years postoperatively.

The typical patient journey was described in a 3-stage model of auditory performance over time, taking into account the factors above (fig. 1). The first stage corresponded to the period of normal hearing in a postlinguis-

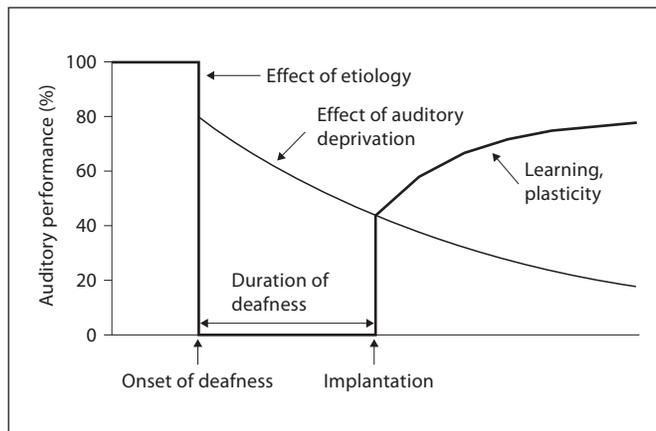


Fig. 1. The 3-stage model of auditory performance over time shows the factors used in the analyses. Reproduced from Blamey et al. [1996] with permission.

tically deaf population with auditory performance of 100% (on a speech perception task, for example). Stage 2 began at the onset of profound hearing loss with a drop in auditory performance, which was assumed to be abrupt. A variable effect of etiology on the potential CI outcome was incorporated into the model. The following evolution encompassed gradual changes of the peripheral and central auditory system, whose effect depended on the duration of auditory deprivation. The third stage corresponded to the period starting from implantation, showing a learning curve that may have reflected several factors such as devices, speech processing strategies, surgical trauma and surgical placement of the electrode array, existence and type of rehabilitation, and cerebral reorganization.

Even though this model and the factors considered by Blamey et al. [1996] are still relevant, the model may be improved and better understood in the light of new findings. Indeed, the development of improved neurofunctional investigations has led, for example, to better understanding of auditory cortex maturation in prelinguistic deafness [Finney et al., 2001; Lee et al., 2001] and of cognitive factors that may influence CI outcome in postlinguistic deafness [Lazard et al., 2010b, 2011; Lee et al., 2007; Strelnikov et al., 2010]. These new findings in postlinguistic deafness research may improve the description of auditory performance proposed in the model.

Moreover, many factors have changed substantially since 1996 and may influence outcomes in different ways. In the intervening 15 years, CI eligibility requirements have become less restrictive. In 1996, the majority of the

patients being implanted were bilaterally profoundly deaf, i.e. the PTA threshold at 500, 1000, and 2000 Hz was greater than 90 dB HL and their preoperative open-set sentence recognition score with best-fitted hearing aids and without lipreading was less than 30% [NIH Consensus Conference, 1995]. Indications were later extended to sentence recognition scores with best-fitted hearing aids less than 60%, following the findings that patients with residual hearing could also benefit from a CI [Cullen et al., 2004; Dooley et al., 1993; Kiefer et al., 1998; Lenarz, 1998; Rubinstein et al., 1999]. These days, bimodal listening, i.e. combining the use of a CI on one side and the use of a hearing aid on the other ear [Armstrong et al., 1997] or on the same ear [Hodges et al., 1997], is widely recommended for CI recipients with residual hearing [Ching et al., 2004; Firszt et al., 2008; Gifford et al., 2010]. Access to information has changed dramatically with the advent of the Internet, providing greater awareness of rehabilitation opportunities. The proportion of candidates for a CI with long durations of profound deafness should be smaller, because patients are being operated on earlier in the time course of their deafness. Thus, compared to the 1996 study, the proportion of speech scores in the high range, preoperatively and postoperatively, is likely to be greater nowadays, and the effect of duration of severe to profound deafness may be less strong in the CI population in light of greater residual hearing and improved hearing aid technology prior to cochlear implantation [Blamey, 2005; Johnson et al., 2010; McDermott, 2011].

Nowadays, meningitis (bacterial labyrinthitis) and temporal bone fracture are considered 'surgical emergencies'. The surgery is preferably performed within the month following the disease in order to insert the electrode array before the occurrence of cochlear ossification that would compromise a full insertion [Durisin et al., 2010]. The outcome for patients presenting with these two etiologies is likely to have improved compared to 1996, due to improved screening, less ossification, and deeper insertion.

It is also likely that the proportion of patients older than 70 and even 80 years at the time of their CI operation is greater in 2011. The improvements in anesthesiology [Coelho et al., 2009], the standardization and reduction of the time required for the surgical procedure [Loh et al., 2008; Mack et al., 2006] may have simplified the whole procedure, extending the indications to more fragile patients.

The surgical procedure has been improved due to better knowledge of the histological modifications and trauma it may induce [Handzel et al., 2006; Somdas et al.,

2007], and better knowledge of the importance of electrode array placement within the scala tympani versus the scala vestibuli [Finley et al., 2008; Skinner et al., 2002], leading to the concept of 'soft surgery' [Fraysse et al., 2006; Friedland and Runge-Samuelson, 2009]. These modifications in medical practice should result in fewer extremely poor performers and in better retention of residual hearing in the implanted ear [Fraysse et al., 2006].

Finally, devices have improved in the last 15 years. In the 1996 article, the coding strategies used by the patients were F0F2, F0F1F2 and MPEAK. These strategies are not used anymore and have been replaced by continuous interleaved sampling, and spectral maxima (ACE or N-of-M) strategies [Loizou, 2006]. Other sound processing has been added, such as ADRO[®] (adaptive dynamic range optimization) that selects the most information-rich part of the signal and restores it to the optimal part of the listener's dynamic range [Blamey, 2005]. Other modifications in stimulation rates [Di Lella et al., 2010] or settings [James et al., 2003] have been implemented by each manufacturer, bringing improvements in outcomes [Firszt et al., 2009; Lazard et al., 2010a]. Such modifications, by easing central deciphering of CI stimulation of the auditory nerve, should result in better speech understanding in the whole of the CI population, with a shift of the distribution toward higher speech perception scores.

The aim of the present study was to explore the effects listed above in a larger group of more recent CI recipients using the same methods, model, and statistical analysis as in the 1996 article.

Methods

This project was approved by the Royal Victorian Eye and Ear Hospital Human Research Ethics Committee (Project 10/977H, Multicentre Study of Cochlear Implant Performance in Adults). Fifteen centers from Australia, Europe, and North America participated, the coauthors generously providing access to the records from their clinics.

Retrospective data from 2251 patients were collected. Selection criteria, similar to the 1996 study, were:

- adult at the time of implantation. The youngest patient included was 17 years old when implanted;
- onset of severe to profound hearing loss after the age of 15, for equivalent speech and language acquisition across subjects. The definition for severe to profound hearing loss was as in Lazard et al. [2010b, 2011]. It referred to the time from when the patient could no longer use hearing alone to communicate (i.e. without lipreading), even with the best-fitted hearing aids, and/or understand TV, and/or stopped using the telephone. This definition implicitly included consideration of PTA, but not explicitly, because of the discordance between PTA and

speech recognition abilities sometimes observed in clinical practice. This discordance is particularly obvious for patients with auditory neuropathy spectrum disorder (ANS) [Deltenre et al., 1997; Rance et al., 1999]. When the onset of deafness was different for the two ears, the shorter duration was chosen, i.e. the time when all useful auditory input to the central auditory system ceased. The dates of onset for each ear were estimated by practitioners within each clinic;

- four brands of CIs were included (Advanced Bionics, Cochlear, Med-el, and Neurelec). Their proportions in the sample were 21, 50, 17, and 7%, respectively (plus 5% missing data for this variable);
- date of implantation after 2002 for all recipients to ensure technical improvements comparable across brands.

Two postoperative speech intelligibility scores in quiet for each recipient were requested from the clinics: one score collected early after activation of the CI (T1) and one score collected later (T2). The choice of the date of the tests was free and varied between and within centers. However, within each center, all the subjects were tested with the same test material. In total, 3787 speech perception test scores in quiet were received (1934 for T1 and 1853 for T2).

Statistical Analyses

As in the 1996 study, the fundamental assumptions behind the analysis were that the patient groups from each center were independent but similar samples from the same population, and that the different auditory performance measures and languages used in each clinic would not affect the rank ordering of patient scores from lowest to highest. Figure 2 shows 4 examples of preoperative and postoperative score distributions for different auditory performance measures used by some clinics. To combine different speech test scores in quiet (phonemes, monosyllabic words, disyllabic words, sentences) in different languages and different levels of presentation (from 55 to 75 dB SPL), a percentile rank for each patient within each center was calculated from the speech test scores. In order to include the effect of CI experience (i.e. the effect of time postoperatively), the scores at T1 and T2 were both incorporated in the rankings. Using ranking removes differences in clinical practice without removing the relative differences between patients within each clinic. Indeed, for each clinic, the distribution varied uniformly from 0 to 100. The best performers from each center had a percentile rank close to 100, and the poorest performers from each group had a percentile rank close to 0. The ranked data of the centers were combined for the global analysis. For further details on ranking, please refer to Blamey et al. [1996].

Similarly to the 1996 analysis, the same independent factors were chosen and partitioned into ranges (although note that the definitions of the onset of severe to profound hearing loss were slightly different). The means of the ranges were compared by applying a 4-factor unbalanced analysis of variance using the general linear model (GLM; Minitab version 12). The first factor was *duration of severe to profound hearing loss* defined as the time in years between the onset of severe to profound hearing loss and the date of implantation. The ranges for duration of severe to profound hearing loss were 0–4, 5–9, 10–14, 15–19, 20–24, 25–34, 35–44 and over 45 years. The second factor, *age at onset of severe to profound hearing loss*, was split into the ranges 15–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80 years or over. The classification for age at onset was slightly different from the 1996 classifica-

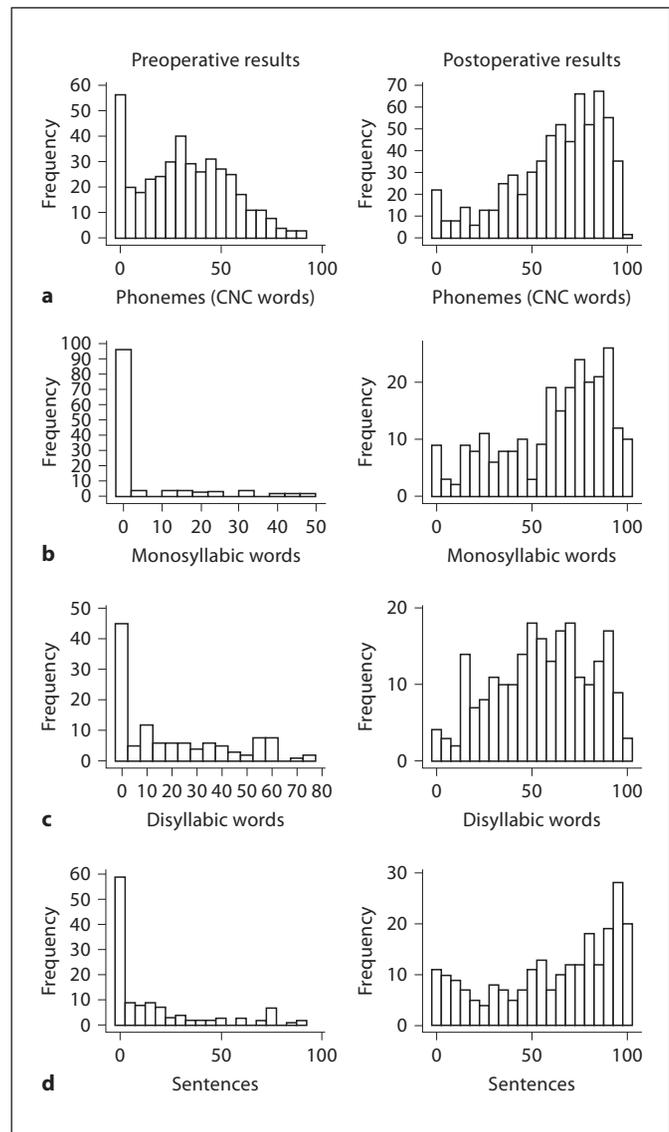


Fig. 2. Each center used a different speech perception test and presentation level as the measure of auditory performance. Example distributions of preoperative and postoperative scores from individual centers are shown for: phoneme scores in CNC words presented at 65 dB SPL (a); monosyllabic words presented at 70 dB SPL (b); disyllabic words presented at 60 dB SPL (c), and sentences presented at 70 dB SPL (d).

tion in which the first 2 ranges were 0–9 and 10–19 and stopped at 70 years or over. *Duration of implant experience* was defined as the time elapsed between the date of first activation and the dates of testing (T1 and T2). It was divided into the same ranges as in the 1996 analysis, i.e. 0–5, 6–11, 12–23, 24–35, 36–47, and over 47 months. Classes of *etiologies* were slightly different from the previous analysis. ‘Autoimmune’ and ‘viral labyrinthitis’ etiologies were regrouped into ‘labyrinthitis’ because the differences in etio-

Table 1. Analyses of variance

Factor	Degrees of freedom	Max F	Min p	Min F	Max p
<i>Age at CI</i>					
CI experience	5	15.61	0.000	12.75	0.000
Age at CI	6	9.96	0.000	7.80	0.000
Duration of s/p HL	7	2.89	0.005	2.10	0.041
Etiology	14	1.96	0.017	1.25	0.230
Error	1823				
Total	1855				
<i>Age at onset of severe to profound hearing loss</i>					
CI experience	5	20.67	0.000	12.03	0.000
Age at onset of s/p HL	6	11.97	0.000	8.26	0.000
Duration of s/p HL	7	7.00	0.000	4.82	0.000
Etiology	14	1.84	0.028	1.70	0.050
Error	1823				
Total	1855				

When data points were available for both the early (T1) and late (T2) testings, only one testing was chosen randomly and included in the analysis. Five different randomizations were tested and the maximum and minimum F and p values are listed for each independent variable across the 5 randomizations. Separate analyses were conducted with age at CI and age at onset of severe to profound hearing loss as independent factors. s/p HL = Severe to profound hearing loss.

pathology of these 2 diseases are not perfectly understood and these subgroups displayed similar performance in the 1996 dataset. To avoid confusion, 'bacterial labyrinthitis' was renamed 'meningitis'. The 'traumatic' etiology was split into 3 new groups: 'temporal bone fracture', 'acoustic trauma' and 'pressure trauma', as the consequences for nerve survival and ossification are not necessarily the same for all traumata [Kujawa and Liberman, 2009; Serin et al., 2010]. As 'congenital syphilis' was not reported in the new dataset, this etiology was omitted. Four new categories were added to the list of etiologies in the 1996 study: 'auditory neuropathy spectrum disorder (ANSO)' (diagnosed on clinical and electrophysiological features), 'chronic otitis media', 'acoustic neuroma' (regrouping isolated cases or those included in a neurofibromatosis), and 'miscellaneous'. 'Miscellaneous' included non-genetic congenital etiologies, cerebral ischemia, drepanocytosis, and cephalic trauma without temporal bone fracture, among others. The final factor, *age at implantation*, was partitioned as follows: 17–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80 years or over. The oldest group (80 years or over) was added, compared to the 1996 analysis, because of broadened inclusion criteria in the past 10 years. Because *age at implantation* is equal to the sum of *age at onset of severe to profound hearing loss* and *duration of severe to profound hearing loss*, at most 2 of these 3 variables should be included in a single statistical analysis to avoid violating the requirement for independent factors. For this reason, 2 GLM analyses were performed excluding one or the other age factor. The results are detailed in the Results section.

The dependent variable used for the GLM analyses was the percentile ranked score. In total, 1856 patients had complete data for the independent variables listed above and at least 1 ranked

score at T1 and/or T2. Technically, a repeated-measures analysis should be used for these data since there were ranked scores for both T1 and T2 for most subjects. Our statistics software was unable to analyze an unbalanced repeated-measures design for 1856 subjects, and so the design was simplified by selecting only 1 ranked score for each subject. When there were ranked scores for both T1 and T2, 1 was chosen randomly. Five different randomizations were performed for each analysis and the range of statistical results is reported in table 1.

Data from the 1996 analysis were not available for specific statistical comparisons, such as modifications of clinical characteristics (e.g. amount of residual hearing in the two samples, and hearing aid use).

Results

The mean age at implantation per center ranged from 48 to 65 years, and the mean duration of severe to profound hearing loss per center ranged from 2 to 13 years.

The ANOVA statistics for two analyses are shown in table 1. Similarly to the 1996 analysis, all tested factors had a significant main effect (table 1). Nevertheless, the relative influence of each factor was different from the 1996 study. In 1996, duration of severe to profound hearing loss accounted for more of the variance than the other factors. Then came age at onset of severe to profound hearing loss

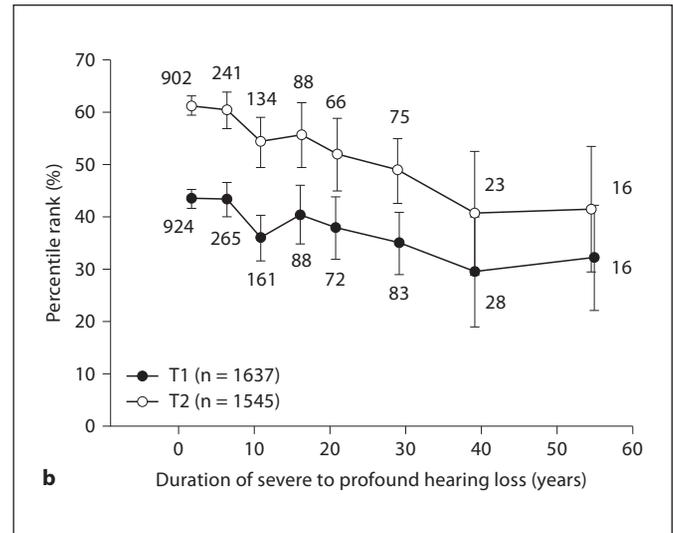
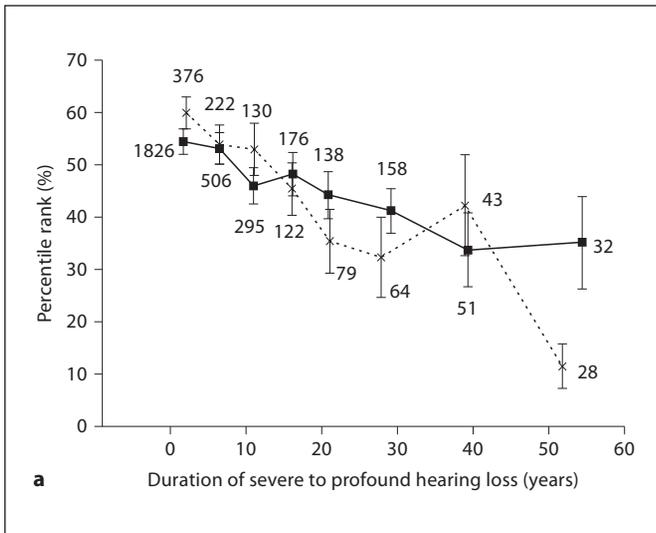


Fig. 3. a Duration of severe to profound hearing loss had a significant effect on percentile rank in the 1996 study (dashed lines and crosses) and in the current study (solid lines and squares). Error bars indicate ± 2 standard errors of the mean for each duration range. The numbers next to each symbol indicate the number of scores contributing to the mean for that duration range.

b The improvement in performance (percentile rank) over time became smaller with longer duration of severe to profound hearing loss. Error bars indicate ± 2 standard errors of the mean for each duration range. The numbers next to each symbol indicate the number of data points contributing to the mean for that duration range.

or age at implantation, etiology, and finally duration of CI experience. In 2011, duration of CI experience had the largest effect (F ranged from 12.03 to 20.67, from the 5 different randomizations), followed by age at onset of severe to profound hearing loss or age at implantation, duration of severe to profound hearing loss, and etiology. The 4 factors accounted for an average of 9.5% of the variance using age at implantation as a factor and 10.5% of the variance using age at onset of severe to profound hearing loss as a factor. These percentages were calculated as: (total sum of squares – error sum of squares)/total sum of squares.

For convenience, the description of the results for each factor follows in the order used in 1996, and the graphs compare the older and newer data directly. Wherever possible, the complete dataset of 3787 ranked scores was used in the graphs, and the numbers on the graphs refer to the number of data points, not the number of subjects.

Duration of Severe to Profound Hearing Loss

Figure 3a shows the averaged percentile rank as a function of duration of severe to profound hearing loss for results from the 1996 and 2011 analyses. A negative influence of duration of severe to profound hearing loss was observed in both studies, but it was less important in 2011 than in 1996, with a 19% difference between the two

extreme ranges in 2011 versus 48% in 1996, mainly due to the dramatic drop for durations of more than 45 years observed in 1996 but not observed in 2011. Mean percentile ranks of this subgroup (durations of more than 45 years) were not significantly different from the 35- to 44-year subgroup in 2011.

Averaged percentile ranks for the 2011 dataset were subsequently graphed separately for times of testing (T1 and T2; fig. 3b). On average, the range of time of testing for T1 was 0.3–0.6 years, and the range of time of testing for T2 was 1.2–2 years. The groups with the smallest durations of severe to profound hearing loss were tested at 0.5 (T1) and 2 (T2) years, on average, and the groups with the longest durations of severe to profound hearing loss were tested at 0.5 (T1) and 1.3 (T2) years, on average. The graphic representation shows that the amount of gain in performance between T1 and T2 is smaller in case of longer durations of severe to profound hearing loss: +17.8% for the group with the shortest durations of severe to profound hearing loss and +9.4% for the group with the longest durations of severe to profound hearing loss. The smaller gain in performance may have been partially due to the shorter period of CI experience in the recipients with long durations of severe to profound hearing loss. The improvement was significantly greater than zero for patients presenting

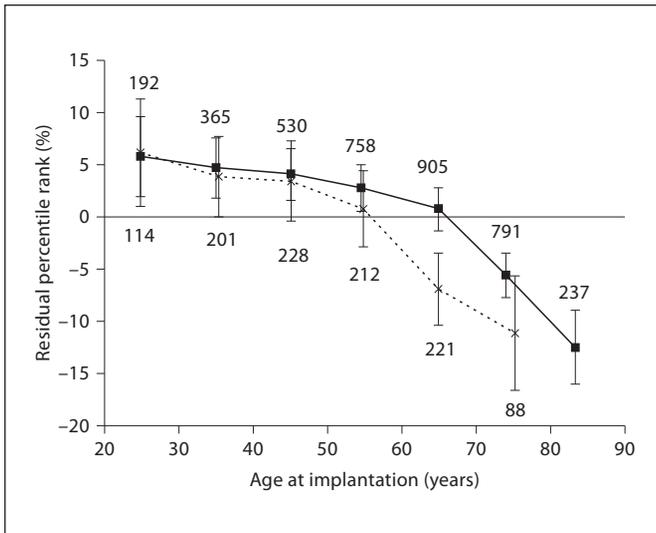


Fig. 4. Age at implantation had a significant effect on the residual percentile rank after accounting for the effect of duration of severe to profound hearing loss for people over the age of 60 years in 1996 (dashed lines and crosses). There was a significant effect of age at implantation for people over age 70 years in the current study (solid lines and squares). Residual percentile rank represents the amount of performance explained after allowing for the influence of the other factors. Error bars indicate ± 2 standard errors of the mean for each age range. The numbers next to each symbol indicate the number of scores contributing to the mean for that age range.

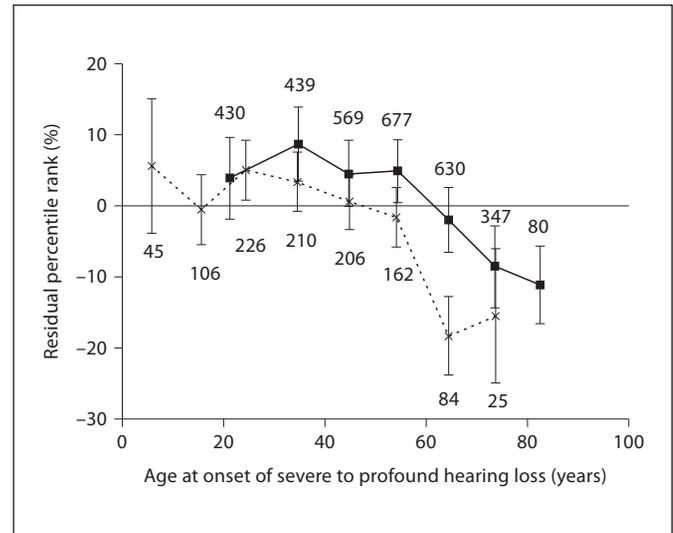


Fig. 5. Age at onset of severe to profound hearing loss had a significant effect on the residual percentile rank after accounting for the effect of duration of severe to profound hearing loss for people over the age of 60 years in 1996 (dashed lines and crosses). There was a significant effect of age at onset of severe to profound hearing loss in the current study (solid lines and squares). Residual percentile rank represents the amount of performance explained after allowing for the influence of the other factors. Error bars indicate ± 2 standard errors of the mean for each age range. The numbers next to each symbol indicate the number of scores contributing to the mean for that age range.

with durations of severe to profound hearing loss of less than 30 years, while it was not for patients with longer durations. The error bars extending ± 2 standard errors are approximately equivalent to the 95% confidence interval for each mean value shown on the graph. The confidence intervals for patients presenting with long durations of severe to profound hearing loss were wider due to the smaller numbers of data points contributing to the mean values.

Age at Implantation

Age at implantation had a negative influence on the outcomes for ages over 60 years in 1996, and for ages over 70 years in 2011 (fig. 4). The shapes of the performance versus age at implantation curves were similar in the two studies but the effect of age was delayed by about 10 years in the more recent study. Age at implantation accounted for about 2.9% of the variance in the 2011 data. A greater number of older patients (70+ years) were being implanted in 2011 than in the 1996 study. They represented 8% in 1996 versus 28% in 2011 (21% for the range 70–79 years and 7% for 80+ years).

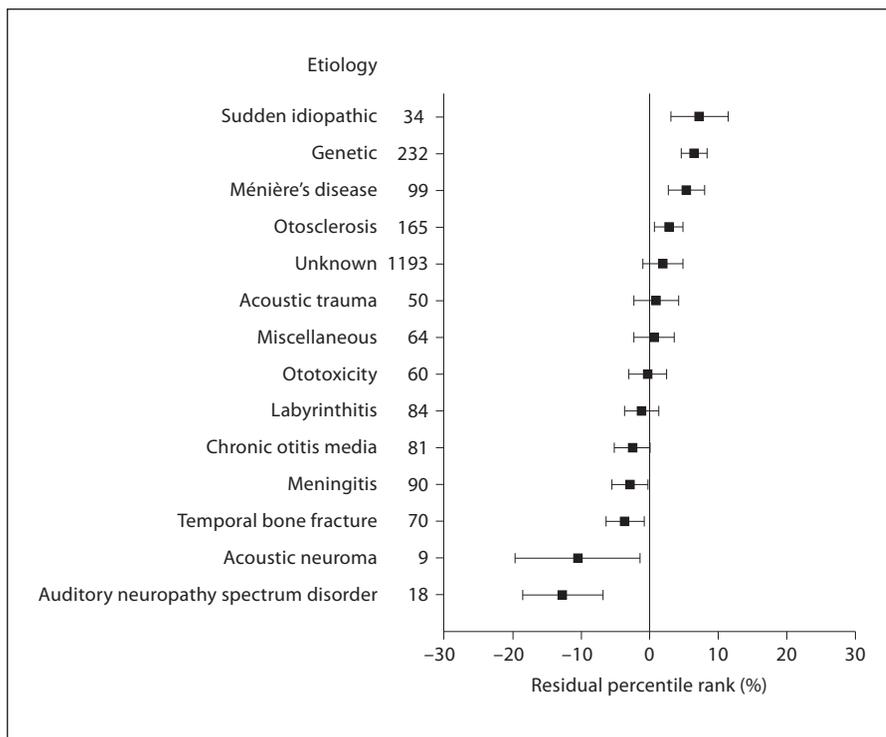
Age at Onset of Severe to Profound Hearing Loss

Increasing age at onset of severe to profound hearing loss from 15 to 79 years yielded 21% decrease in performance in 1996 and 11% in 2011 (fig. 5), the group 60–69 years performing significantly better in 2011 than in 1996. A significant drop in outcome was observed in 1996 for the range 60–69 years. In 2011, this drop was significant from 70 years onwards. The average age for the range 70–79 years of the 2011 analysis was the same as the range 70 years and over of the 1996 analysis, while a new category (80+ years) was added in 2011. The effect of age at onset appears to be delayed by about 10 years in the 2011 dataset compared to the 1996 dataset. Age at onset of severe to profound hearing loss accounted for about 3.3% of the variance in the 2011 data.

Etiology

Figure 6 shows the mean residual percentile rank for each etiology. The ‘unknown etiology’ group was by far the largest, including about 50% of the patients in 1996 and 2011. The ANSD subgroup performed significantly

Fig. 6. Etiology had a significant effect on the residual percentile rank in the current study. Error bars indicate ± 2 standard errors of the mean for each etiology. Residual percentile rank represents the amount of performance explained after allowing for the influence of the other factors. The numbers next to each etiology indicate the number of patients in that etiology. Results for pressure trauma are not presented because there were only 2 cases in this group.



below the average of all etiologies ($p = 0.03$), while the genetic and Ménière's disease groups performed above the average ($p = 0.001$ and $p = 0.04$, respectively). The Ménière's disease group also performed significantly better than average in 1996. Meningitis patients performed close to average in 2011, while they performed lower than average in 1996. The three subgroups for cochlear ossification, labyrinthitis, meningitis, and temporal bone fracture performed similarly to each other in 2011.

Duration of Implant Experience

Performance increased as a function of duration of implant experience up to 3.5 years after implantation (fig. 7). The amount of improvement was about 10% in 1996 and 20% in 2011, with a steeper slope within the first year of experience. CI experience was the most significant factor in the analyses with the largest F values in 2011 [$12.03 < F(5, 1823) < 20.67$ in the 5 different randomizations, $p < 0.001$], and one of the least significant factors in 1996 [$F(5, 1033) = 3.66$, $p = 0.003$]. The slight decrease in performance observed after 5 years of CI use in 2011 was not statistically significant.

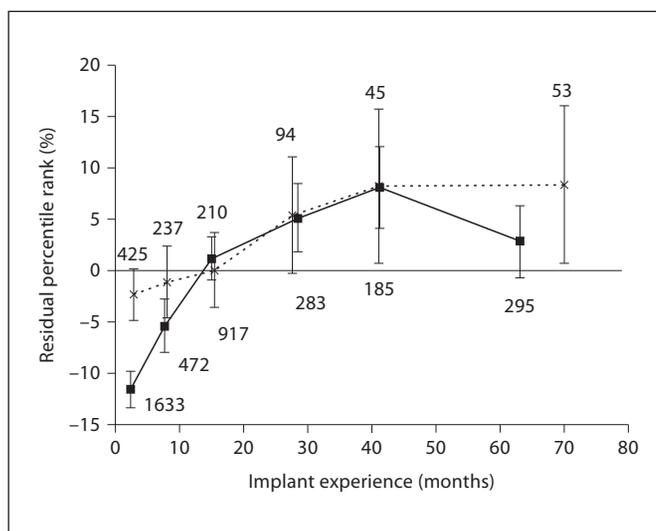


Fig. 7. CI experience (date of testing minus date of first activation) had a significant effect on the residual percentile rank after accounting for the effects of other factors in 1996 (dashed lines and crosses) and in the current study (solid lines and squares). Residual percentile rank represents the amount of performance explained after allowing for the influence of the other factors. Error bars indicate ± 2 standard errors of the mean for each CI experience range. The numbers next to each symbol indicate the number of scores contributing to the mean at that CI experience range.

Discussion

The present study aimed to update and compare the results of a previously published study [Blamey et al., 1996] about predictors of auditory performance of post-linguistically deaf adults receiving a CI. Similarly to the 1996 study, percentile ranking of speech scores was used in order to combine data from different centers. However, as in 1996, the assumption that the patient groups from each center were similar samples from the same population may not be applicable for all the factors. For example, the mean age at implantation and the mean duration of severe to profound hearing loss per center were different, indicating that there may have been significant differences in the populations treated by each center. In this case, the use of ranking may have reduced the natural variation between the samples and therefore reduced the relative effects of some factors, including the effect of age at implantation and duration of severe to profound hearing loss. Constraints imposed by the multicenter nature of these studies make it impossible to check this possible bias, but the effects of the factors are more likely to be underestimated than overestimated in the study, by the use of percentile ranking.

A second caveat arises from the use of separate percentile ranks in 1996 and 2011. This means that equal ranks in 1996 and 2011 do not imply equal speech perception scores and we cannot detect changes in the absolute levels of performance that may have occurred between 1996 and 2011. Therefore, because the raw data from 1996 are no longer available, our discussion is constrained to cover only changes in the relative importance of different factors between 1996 and 2011. We may speculate as to whether these changes in relative importance are due to changes in absolute performance arising from improvements of devices or surgical and medical practices, but direct evidence for such improvements can only come from direct comparison of raw scores for patients implanted at different times, with different devices, and with different surgical techniques [Dowell, 2012; Rubinstein et al., 1999].

Although the factors affecting auditory performance of CI recipients in the earlier study also had statistically significant effects in 2011, the detailed patterns observed in the data were different between the two studies. Before commencing the discussion, we will first consider the basic physiological processes that affect auditory performance and may have given rise to the observed positive and negative effects of the factors in the analyses, and then we will speculate on the possible rea-

sons for the changes in patterns observed between 1996 and 2011.

Table 2 of Blamey et al. [1996] listed the physiological processes affecting auditory performance as: bone growth, malformation, decalcification, disease, trauma and toxicity associated with etiology; natural degeneration of peripheral and central neurons (in their numbers and functions) associated with age; accelerated degeneration of peripheral and central neurons associated with severe to profound hearing loss; plasticity, learning, and protective effects associated with CI experience and with electrical stimulation of the cochlea. All of these physiological processes are still thought to be relevant, although it is becoming clearer that plasticity changes and degeneration of central auditory processing play a much more important role than peripheral factors such as the number of surviving spiral ganglion cells [Moore and Shannon, 2009]. Theoretically, the number and distribution of spiral ganglion cells ought to have a significant effect on basic auditory perception measures [Cohen, 2009]. In 1996, there was no strong evidence that the number of spiral ganglion cells affected CI outcomes, and so far as the authors are aware, no strong evidence has emerged since 1996 [Blamey, 1997; Khan et al., 2005; Nadol and Eddington, 2006]. In contrast, there is strong emerging evidence that central factors such as plasticity and central auditory processing are highly significant [Champoux et al., 2009; Doucet et al., 2006; Giraud and Lee, 2007; Lee et al., 2007; Moore and Shannon, 2009; Rouger et al., 2007; Strelnikov et al., 2010].

The basic effects of the physiological processes are unlikely to have changed between 1996 and 2011. Therefore, the different patterns in the data must be due to differences in the patients in the two studies, improvements in surgical and clinical practice, and/or differences in the CI devices. We speculate that these factors are all needed to explain the data. Patient differences are likely to have arisen because of relaxation of CI patient selection criteria [Cullen et al., 2004; Dooley et al., 1993; Kiefer et al., 1998; Lenarz, 1998; Rubinstein et al., 1999], and because of improvements in the management of hearing loss during stage 2 of the model, such as improvements in hearing aid technology [Blamey, 2005; Johnson et al., 2010; McDermott, 2011]. Evidence for differences between the patients in the two studies can be seen in figure 3a where the median duration of severe to profound hearing loss was about 8 years in the 1996 dataset and 4 years in the 2011 dataset. In figure 5, the median age at onset of severe to profound hearing loss was about 39 years in 1996 and 52 years in 2011. Thus selection criteria in 2011 resulted

in shorter periods of severe to profound hearing loss with later onset in life than in 1996. The changes in hearing loss management are likely to have resulted in a slowing of the degenerative effects of severe to profound hearing loss (presumably at a central level), and the changes in selection criteria are likely to have resulted in a higher average level of auditory processing and less reorganized cognitive function in patients immediately prior to cochlear implantation. These changes could thus account for the reduced effect of duration of severe to profound hearing loss in the 2011 data compared to the 1996 data. Figure 3b shows that patients with longer durations of severe to profound hearing loss tended to improve less between T1 and T2. This may represent increased reorganization of the brain [Lazard et al., 2010b, 2011] and a slowing down of the CI learning curve as a consequence. However, we cannot exclude that the smaller gain in performance may have been partially due to the shorter period of CI experience at T2 in the recipients with long durations of severe to profound hearing loss. It should also be noted that the smaller number of evaluations for recipients with longer severe to profound hearing loss duration reduces the statistical significance of the difference between T1 and T2.

A change in clinical practice is likely to account for difference in the close to average performance of meningitic patients in 2011. The significant negative effect of meningitis, which was labeled as bacterial labyrinthitis in 1996, was based on a sample of 135 patients, many of whom may have had ossification of the cochlea as a consequence of the disease. The 90 patients in the 2011 study are likely to have been implanted very soon after the disease, before ossification took place, and are therefore more likely to have had a better outcome than the 1996 patients [Durisin et al., 2010]. The emergence of ANSD in 2011 as a new etiology with poor outcome occurred because these patients were not identified clinically in 1996 [Deltenre et al., 1997; Rance et al., 1999]. Other differences in the etiology pattern of results are probably due to the larger number of patients and thus greater power in the analysis in 2011.

The effect of age at onset of severe to profound hearing loss reflects the natural processes that occur prior to onset of hearing loss, and is thus presumably less affected by changes in clinical practice. In both datasets, the effect of age at onset begins at around age 60, but the magnitude of the effect was larger in 1996 than in 2011. On the one hand, we may speculate that the amount of natural peripheral and central degradation might have been reduced in 2011 by more frequent use of hearing aids in the

period preceding severe to profound hearing loss, encouraged by improved sound quality and speech understanding [Blamey, 2005; Johnson et al., 2010; McDermott, 2011]. Alternatively, the greater information content and processing improvements in the CI devices used by the 2011 group may have imposed less cognitive and auditory processing load than the earlier devices and therefore the effects of natural cognitive degradation were reduced for the 2011 group. A similar argument may explain the 10-year delay in the effect of age at implantation. If these speculations are correct, it appears that the average reduction in the cognitive and auditory processing load for the newer devices is equivalent to the average amount of cognitive and auditory processing degradation that occurs naturally in 10 years after the age of 60 years.

The most striking difference between the 1996 and 2011 studies is the greater and faster improvement in post-operative auditory performance observed in 2011. This change is most likely due to improvements in sound processing and in the implant devices themselves, as well as the greater average capacity of the population of implant patients to take advantage of the new auditory information provided by the devices. For example, Dowell [2012] indicates an improvement in open-set sentence scores from less than 40% for sound processors used in the 1990s to more than 80% for modern sound processors. The corresponding improvements for CNC words were from 40 to 70%. Preserving the anatomical structures may also have contributed to the improvements in surgical management (soft surgery [Frayse et al., 2006; Friedland and Runge-Samuelson, 2009]). The slight decrease in performance after 5 years of CI experience represents patients who had been operated on before 2005. They may not have benefited from the most recent improvements in coding strategies [Zeng, 2011] and in surgical techniques [Friedland and Runge-Samuelson, 2009].

The difference in total variance explained in the two studies (21% in Blamey et al. [1996] and 10% in the present study) may be explained by the smaller influence of some of the factors, as detailed earlier, and the possibly greater random variance in the 2011 study, due to the inclusion of more centers. A large proportion of the residual variance may be due to inherent test/retest variability in the materials used, which typically have a relatively small number of items per list; however, there are obviously many potential factors that have not been included in the model used in this study. The influence of new factors, such as hearing aid use, residual hearing, influence of duration of moderate hearing loss, will be studied in a separate study [Lazard et al., in press].

Conclusions

Five of the main factors influencing individual differences in auditory performance of CI recipients in 1996 still had significant effects in 2011, although the detailed pattern of results and the relative importance of the factors had changed. CI experience became the most significant factor and the relative effects of duration of deafness and age reduced. The changes between 1996 and 2011 are likely due to relaxed patient selection criteria, improved clinical management of hearing loss, modifications of surgical practice, and improved devices. Durations of severe to profound hearing loss of more than 40 years negatively influenced performance, but this effect then stabilized, possibly because of fixed central reorganizations. Patients implanted after 75 years of age performed poorly compared to younger recipients, but it is well known that older patients still receive significant improvement in life quality and maintain independence

once implanted. The use of hearing aid before the period of severe to profound hearing loss may dampen the cognitive changes that appear with age, and should be encouraged. The influence of new factors, such as hearing aid use, residual hearing, influence of duration of moderate hearing loss, will be included in a new model of auditory performance and central evolution over time [Lazard et al., in press].

Acknowledgements

Salomé Fontollet is acknowledged for her contribution in collecting a great amount of data for the Quebec Cochlear Implant Program, Canada. The authors also want to thank Elise Billoir for her valuable advice in the statistical analyses. The Bionics Institute acknowledges the support it receives from the Victorian Government through its Operational Infrastructure Support Program. Dr. Lazard's funding was provided by the Fondation Bettencourt-Schueller (Prix des Jeunes Chercheurs 2010), without any conflict of interest.

References

- Armstrong M, Pegg P, James C, Blamey P: Speech perception in noise with implant and hearing aid. *Am J Otol* 1997;18:S140–S141.
- Blamey P: Are spiral ganglion cell numbers important for speech perception with a cochlear implant? *Am J Otol* 1997;18:S11–S12.
- Blamey PJ: Adaptive dynamic range optimization (ADRO): a digital amplification strategy for hearing aids and cochlear implants. *Trends Amplif* 2005;9:77–98.
- Blamey P, Arndt P, Bergeron F, Bredberg G, Brimacombe J, Facer G, Larky J, Lindstrom B, Nedzelski J, Peterson A, Shipp D, Staller S, Whitford L: Factors affecting auditory performance of postlinguistically deaf adults using cochlear implants. *Audiol Neurootol* 1996;1:293–306.
- Champoux F, Lepore F, Gagne JP, Theoret H: Visual stimuli can impair auditory processing in cochlear implant users. *Neuropsychologia* 2009;47:17–22.
- Ching TY, Incerti P, Hill M: Binaural benefits for adults who use hearing aids and cochlear implants in opposite ears. *Ear Hear* 2004;25:9–21.
- Coelho DH, Yeh J, Kim JT, Lalwani AK: Cochlear implantation is associated with minimal anesthetic risk in the elderly. *Laryngoscope* 2009;119:355–358.
- Cohen LT: Practical model description of peripheral neural excitation in cochlear implant recipients. 4. Model development at low pulse rates: general model and application to individuals. *Hear Res* 2009;248:15–30.
- Cullen RD, Higgins C, Buss E, Clark M, Pillsbury HC 3rd, Buchman CA: Cochlear implantation in patients with substantial residual hearing. *Laryngoscope* 2004;114:2218–2223.
- Deltenre P, Mansbach AL, Bozet C, Clercx A, Hecox KE: Temporal distortion products (kernel slices) evoked by maximum-length sequences in auditory neuropathy: evidence for a cochlear pre-synaptic origin. *Electroencephalogr Clin Neurophysiol* 1997;104:10–16.
- Di Lella F, Bacciu A, Pasanisi E, Vincenti V, Guida M, Bacciu S: Main peak interleaved sampling (MPIS) strategy: effect of stimulation rate variations on speech perception in adult cochlear implant recipients using the Digisonic SP cochlear implant. *Acta Otolaryngol* 2010;130:102–107.
- Dooley GJ, Blamey PJ, Seligman PM, Alcantara JI, Clark GM, Shallop JK, Arndt P, Heller JW, Menapace CM: Combined electrical and acoustical stimulation using a bimodal prosthesis. *Arch Otolaryngol Head Neck Surg* 1993;119:55–60.
- Doucet ME, Bergeron F, Lassonde M, Ferron P, Lepore F: Cross-modal reorganization and speech perception in cochlear implant users. *Brain* 2006;129:3376–3383.
- Dowell RC: Evidence about effectiveness of cochlear implants in adults; in Wong L, Hickson L (eds): Evidence-Based Practice in Audiology. San Diego, Singular Publishing, 2012.
- Durisin M, Bartling S, Arnoldner C, Ende M, Prokein J, Lesinski-Schiedat A, Lanfermann H, Lenarz T, Stover T: Cochlear osteoneogenesis after meningitis in cochlear implant patients: a retrospective analysis. *Otol Neurotol* 2010;31:1072–1078.
- Finley CC, Holden TA, Holden LK, Whiting BR, Chole RA, Neely GJ, Hullar TE, Skinner MW: Role of electrode placement as a contributor to variability in cochlear implant outcomes. *Otol Neurotol* 2008;29:920–928.
- Finney EM, Fine I, Dobkins KR: Visual stimuli activate auditory cortex in the deaf. *Nat Neurosci* 2001;4:1171–1173.
- Firszt JB, Holden LK, Reeder RM, Skinner MW: Speech recognition in cochlear implant recipients: comparison of standard hires and hires 120 sound processing. *Otol Neurotol* 2009;30:146–152.
- Firszt JB, Reeder RM, Skinner MW: Restoring hearing symmetry with two cochlear implants or one cochlear implant and a contralateral hearing aid. *J Rehabil Res Dev* 2008;45:749–767.
- Frayssse B, Macias AR, Sterkers O, Burdo S, Ramsden R, Deguine O, Klenzner T, Lenarz T, Rodriguez MM, Von Wallenberg E, James C: Residual hearing conservation and electroacoustic stimulation with the nucleus 24 contour advance cochlear implant. *Otol Neurotol* 2006;27:624–633.
- Friedland DR, Runge-Samuels C: Soft cochlear implantation: rationale for the surgical approach. *Trends Amplif* 2009;13:124–138.

- Gifford RH, Dorman MF, Shallop JK, Sydlowski SA: Evidence for the expansion of adult cochlear implant candidacy. *Ear Hear* 2010;31:186–194.
- Giraud AL, Lee HJ: Predicting cochlear implant outcome from brain organisation in the deaf. *Restor Neurol Neurosci* 2007;25:381–390.
- Green KM, Bhatt YM, Mawman DJ, O'Driscoll MP, Saeed SR, Ramsden RT, Green MW: Predictors of audiological outcome following cochlear implantation in adults. *Cochlear Implants Int* 2007;8:1–11.
- Handzel O, Burgess BJ, Nadol JB Jr: Histopathology of the peripheral vestibular system after cochlear implantation in the human. *Otol Neurotol* 2006;27:57–64.
- Hodges AV, Schloffman J, Balkany T: Conservation of residual hearing with cochlear implantation. *Am J Otol* 1997;18:179–183.
- James CJ, Skinner MW, Martin LF, Holden LK, Galvin KL, Holden TA, Whitford L: An investigation of input level range for the nucleus 24 cochlear implant system: speech perception performance, program preference, and loudness comfort ratings. *Ear Hear* 2003;24:157–174.
- Johnson JA, Cox RM, Alexander GC: Development of APHAB norms for WDRC hearing aids and comparisons with original norms. *Ear Hear* 2010;31:47–55.
- Khan AM, Handzel O, Burgess BJ, Damian D, Eddington DK, Nadol JB Jr: Is word recognition correlated with the number of surviving spiral ganglion cells and electrode insertion depth in human subjects with cochlear implants? *Laryngoscope* 2005;115:672–677.
- Kiefer J, von Ilberg C, Reimer B, Knecht R, Gall V, Diller G, Sturzebecher E, Pfennigdorff T, Spelsberg A: Results of cochlear implantation in patients with severe to profound hearing loss – Implications for patient selection. *Audiology* 1998;37:382–395.
- Kujawa SG, Liberman MC: Adding insult to injury: cochlear nerve degeneration after 'temporary' noise-induced hearing loss. *J Neurosci* 2009;29:14077–14085.
- Lazard DS, Bordure P, Lina-Granade G, Magnan J, Meller R, Meyer B, Radafy E, Roux PE, Gnansia D, Pean V, Truy E: Speech perception performance for 100 post-lingually deaf adults fitted with neurelec cochlear implants: comparison between Digisonic® convex and Digisonic® SP devices after a 1-year follow-up. *Acta Otolaryngol* 2010a;130:1267–1273.
- Lazard DS, Giraud AL, Truy E, Lee HJ: Evolution of non-speech sound memory in postlingual deafness: implications for cochlear implant rehabilitation. *Neuropsychologia* 2011;49:2475–82.
- Lazard DS, Lee HJ, Gaebler M, Kell CA, Truy E, Giraud AL: Phonological processing in postlingual deafness and cochlear implant outcome. *Neuroimage* 2010b;49:3443–3451.
- Lazard DS, Vincent C, Venail F, Van de Heyning P, Truy E, Sterkers O, Skarzynski PH, Skarzynski H, Schauwers K, O'Leary S, Mawman D, Maat B, Kleine-Punte A, Huber AM, Green K, Govaerts PJ, Fraysse B, Dowell R, Dillier N, Burke E, Beynon A, Bergeron F, Başkent D, Artières F, Blamey PJ: Pre-, per- and postoperative factors affecting performance of postlingually deaf adults using cochlear implants: a new conceptual model over time. *PLoS One*, in press.
- Lee DS, Lee JS, Oh SH, Kim SK, Kim JW, Chung JK, Lee MC, Kim CS: Cross-modal plasticity and cochlear implants. *Nature* 2001;409:149–150.
- Lee HJ, Giraud AL, Kang E, Oh SH, Kang H, Kim CS, Lee DS: Cortical activity at rest predicts cochlear implantation outcome. *Cereb Cortex* 2007;17:909–917.
- Lenarz T: Cochlear implants: selection criteria and shifting borders. *Acta Otorhinolaryngol Belg* 1998;52:183–199.
- Loh C, Jiang D, Dezso A, Fitzgerald O'Connor A: Non-sutured fixation of cochlear implants using a minimally-invasive approach. *Clin Otolaryngol* 2008;33:259–261.
- Loizou PC: Speech processing in vocoder-centric cochlear implants. *Adv Otorhinolaryngol* 2006;64:109–143.
- Mack KF, Heermann R, Issing PR, Lenarz T, Schwab B: Four years' experience with the minimally invasive surgical approach in cochlear implant surgery. *Minim Invasive Ther Allied Technol* 2006;15:187–192.
- Matterson AG, O'Leary S, Pinder D, Freidman L, Dowell R, Briggs R: Otosclerosis: selection of ear for cochlear implantation. *Otol Neurotol* 2007;28:438–446.
- McDermott HJ: A technical comparison of digital frequency-lowering algorithms available in two current hearing aids. *PLoS One* 2011; 6:e22358.
- Moore DR, Shannon RV: Beyond cochlear implants: awakening the deafened brain. *Nat Neurosci* 2009;12:686–691.
- Nadol JB Jr, Eddington DK: Histopathology of the inner ear relevant to cochlear implantation. *Adv Otorhinolaryngol* 2006;64:31–49.
- NIH Consensus Conference. Cochlear implants in adults and children. *JAMA* 1995;274:1955–1961.
- Rance G, Beer DE, Cone-Wesson B, Shepherd RK, Dowell RC, King AM, Rickards FW, Clark GM: Clinical findings for a group of infants and young children with auditory neuropathy. *Ear Hear* 1999;20:238–252.
- Rouger J, Lagleyre S, Fraysse B, Deneve S, Deguine O, Barone P: Evidence that cochlear-implanted deaf patients are better multisensory integrators. *Proc Natl Acad Sci USA* 2007;104:7295–7300.
- Rubinstein JT, Parkinson WS, Tyler RS, Gantz BJ: Residual speech recognition and cochlear implant performance: effects of implantation criteria. *Am J Otol* 1999;20:445–452.
- Serin GM, Derinsu U, Sari M, Gergin O, Ciprut A, Akdas F, Batman C: Cochlear implantation in patients with bilateral cochlear trauma. *Am J Otolaryngol* 2010;31:350–355.
- Skinner MW, Ketten DR, Holden LK, Harding GW, Smith PG, Gates GA, Neely JG, Kletzer GR, Brunsten B, Blocker B: CT-derived estimation of cochlear morphology and electrode array position in relation to word recognition in Nucleus-22 recipients. *J Assoc Res Otolaryngol* 2002;3:332–350.
- Somdas MA, Li PM, Whiten DM, Eddington DK, Nadol JB Jr: Quantitative evaluation of new bone and fibrous tissue in the cochlea following cochlear implantation in the human. *Audiol Neurootol* 2007;12:277–284.
- Strelnikov K, Rouger J, Demonet JF, Lagleyre S, Fraysse B, Deguine O, Barone P: Does brain activity at rest reflect adaptive strategies? Evidence from speech processing after cochlear implantation. *Cereb Cortex* 2010;20:1217–1222.
- Yukawa K, Cohen L, Blamey P, Pyman B, Tungvachirakul V, O'Leary S: Effects of insertion depth of cochlear implant electrodes upon speech perception. *Audiol Neurootol* 2004;9:163–172.
- Zeng F-G: Advances in auditory prostheses; in Zeng F, Popper A, Fay R (eds): *Auditory Prostheses: New Horizons*. New York, Springer Handbook of Auditory Research 39, 2011, pp 1–11.

© Free Author Copy – for personal use only

ANY DISTRIBUTION OF THIS ARTICLE WITHOUT WRITTEN CONSENT FROM S. KARGER AG, BASEL IS A VIOLATION OF THE COPYRIGHT.

Written permission to distribute the PDF will be granted against payment of a permission fee, which is based on the number of accesses required. Please contact permission@karger.ch