Variability in Cochlear Implantation Outcomes
in a Large German Cohort with a Genetic Etiology of Hearing Loss

Supplemental Digital Content 5.

S5.1 Statistical post-hoc analysis of cochlear implant outcomes for ten genetic and demographic categories with n = 123 ears.

For this statistical post-hoc analysis, we condensed the 30 genetic and demographic categories shown in Figure 5A into ten broader categories representing the significant outcome categories of the primary analysis, as shown in Figure 5A, and investigated these with 123 ears as items entering the analysis. These ten outcome categories are represented in 5 putative factor groups that each can assume two values. These five putative factor groups are designated as: (1) Gene expression: - neural versus other non-neural genes; (2) age at implantation: 0–6 years of age versus >6 years; (3) onset of hearing loss: congenital versus non-congenital (pre-/peri-/post-lingual); (4) implantation delay (gap): 0–5 years versus >5 years; (5) sequence of implantation: simultaneous bilateral implantation versus subsequent bilateral or monaural only implantation (Figure 5B). The outcome categories are ordered according to known or at least expected effects: the first outcome category of each of the five groups (e.g., neural expression) always corresponds to the expected non-favorable property, and the second outcome category to the expected favorable property. These ten categories were of a reasonably distributed size and contained 23 to 100 ears each.

Distributions of the ten categories were tested for normality using Kolmogoroff-Smirnov and Shapiro-Wilk tests. Based on both tests, all distributions have to be regarded as non-gaussian distributions at the 5% level except for the category neural genes. However, the Shapiro-Wilk test would also reject normality at 5.4% for that category. All ten distributions are shown in Figure S5.2. The obvious property deviating from normality is skewness and apparent outliers, i.e., out- and poor performers.

Post-hoc multiple comparisons were performed using the Kruskal-Wallis test, treating all ten categories as independent factors. 20 out of 45 possible comparisons were significant when corrected for multiple comparisons (Bonferroni). According to Cohen's effect size (Cohen 1992), four of these were strong effects (≥ 0.5 effect size r*), the remaining being middle effects ($0.3 \leq r^* < 0.5$) (see table S5.1).

Pairwise Comparisons of group, sorted by effect size in descending order

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Stat. (z)	Sig.	Adj. Sig.[a]	n	effect size r*	effect type
neural_genes - simult_ears	-203,181	49,060	-4,141	0,000	0,002	53	0,57	strong
neural_genes - gap0_5	208,550	45,045	4,630	0,000	0,000	70	0,55	strong
neural_genes - age0_6	206,959	45,373	4,561	0,000	0,000	68	0,55	strong
neural_genes - congenital	186,848	45,045	4,148	0,000	0,002	70	0,50	strong
gap_gt5 - gap0_5	164,597	32,848	5,011	0,000	0,000	123	0,45	middle
gap_gt5 - age0_6	163,006	33,296	4,896	0,000	0,000	121	0,45	middle
age_gt6 - gap0_5	-159,459	32,687	-4,878	0,000	0,000	125	0,44	middle
age_gt6 - age0_6	157,868	33,137	4,764	0,000	0,000	123	0,43	middle
pp_lingual - gap0_5	151,176	32,848	4,602	0,000	0,000	123	0,41	middle
pp_lingual - age0_6	149,585	33,296	4,493	0,000	0,000	121	0,41	middle
gap_gt5 - simult_ears	-159,228	38,168	-4,172	0,000	0,002	106	0,41	middle
gap_gt5 - congenital	142,895	32,848	4,350	0,000	0,001	123	0,39	middle
age_gt6 - simult_ears	-154,090	38,029	-4,052	0,000	0,003	108	0,39	middle
age_gt6 - congenital	-137,756	32,687	-4,214	0,000	0,001	125	0,38	middle
pp_lingual - simult_ears	-145,807	38,168	-3,820	0,000	0,007	106	0,37	middle
pp_lingual - congenital	129,474	32,848	3,942	0,000	0,004	123	0,36	middle
first_sec_ear - gap0_5	-132,777	31,680	-4,191	0,000	0,002	140	0,35	middle
first_sec_ear - age0_6	131,186	32,144	4,081	0,000	0,002	138	0,35	middle
first_sec_ear - simult_ears	-127,409	37,168	-3,428	0,001	0,033	123	0,31	middle
first_sec_ear - congenital	111,075	31,680	3,506	0,000	0,025	140	0,30	middle

Table S5.1. Significant multiple comparison results for the Kruskal-Wallis test on word recognition scores (WRS_{65}) for ten categories. For a complete version of this table, see file Genetic_CI-outcome_SDC05_123ears.xlsx, sheet SDC6 Kruskal-Wallis-test.

Subsequent analysis was performed using Welch-ANOVA because this test is more robust for inhomogeneous variances. As might have been expected from the primary data as shown in Figure 5A, the strong effects are comparisons of the neural-gene category with the favorable outcomes of the remaining four categories (age at implantation: 0-6 years; hearing loss onset: congenital; delay of implantation: 0-5 years and sequence of implantation: simultaneous bilateral).

Table S5.2 shows parameter estimates of the resultant model. For the ANOVA, the data have been centered by subtracting the median WRS_{65} of 70%. As apparent from table S5.2, five categories (gene expression: neural; age at implantation: > 6 years; hearing loss onset: non-congenital (pre-/peri-/post-lingual); delay of implantation: > 5 years; sequence of implantation: non-simultaneous bilateral or monaural only), all representing the expected detrimental factors leading to poorer performance have highly significant effects ($p \leq 0.001$), accounting for a total of 11.8% of the observed variance. The single strongest category was neural gene expression accounting for 3.1% of the variance. The other expected non-favorable categories

contributed 2.3% for age at implantation: > 6 years, 2.3 % for hearing loss onset: non-congenital (pre-/peri-/post-lingual); 2.4% for delay of implantation: > 5 years; 1.7% for the sequence of implantation: non-simultaneous bilateral or monaural.

Parameter	B	Std. Error	t	Sig. (p-val.)	95% Confidence Interval		Partial Eta Squared	Noncent. Parameter	Observed Power[b]
					Lower Bound	Upper Bound			
Intercept	5.000	4.922	1.016	0.310	-4.667	14.667	0.002	1.016	0.174
age 0-6	0.556	6.354	0.087	0.930	-11.924	13.035	0.000	0.087	0.051
age gt6	-21.859	5.792	-3.774	**0.000**	-33.234	-10.484	**0.023**	3.774	0.965
congenital	-0.638	6.300	-0.101	0.919	-13.011	11.734	0.000	0.101	0.051
first_sec_ears	-18.065	5.661	-3.191	**0.001**	-29.181	-6.948	**0.017**	3.191	0.890
gap 0-5	0.851	6.300	0.135	0.893	-11.522	13.224	0.000	0.135	0.052
gap gt5	-22.632	5.813	-3.893	**0.000**	-34.048	-11.216	**0.024**	3.893	0.973
neural genes	-32.826	7.472	-4.393	**0.000**	-47.500	-18.152	**0.031**	4.393	0.992
other genes	-9.250	5.612	-1.648	0.100	-20.272	1.772	0.004	1.648	0.377
peri-post-lingual	-21.711	5.813	-3.735	**0.000**	-33.127	-10.294	**0.023**	3.735	0.962
simult_ears	0[a]								

a. This parameter is set to zero because it is redundant.
b. Computed using alpha = .05

Table S5.2. Parameter estimates of the Welch ANOVA for centered data of the 10 categories, as plotted by SPSS. Partial eta values for significant effects are shown in bold and account for 11.8% of the variance. Number of entries: n=123 ears.

Figure S5.1 shows the mean WRS_{65} according to the Welch ANOVA for the ten categories and the total cohort ordered in the sequence of their mean values. The overall observation is that all non-favorable categories of these ten condensed groups lead to a considerable risk of poor performance, while the favorable counterparts appear to lead to a higher chance of good or above-average performance, but do not prove to reveal high significance in the statistical analysis (only the category “non-neural other genes” shows at least a trend, contributing to 0.4% to the variance observed).

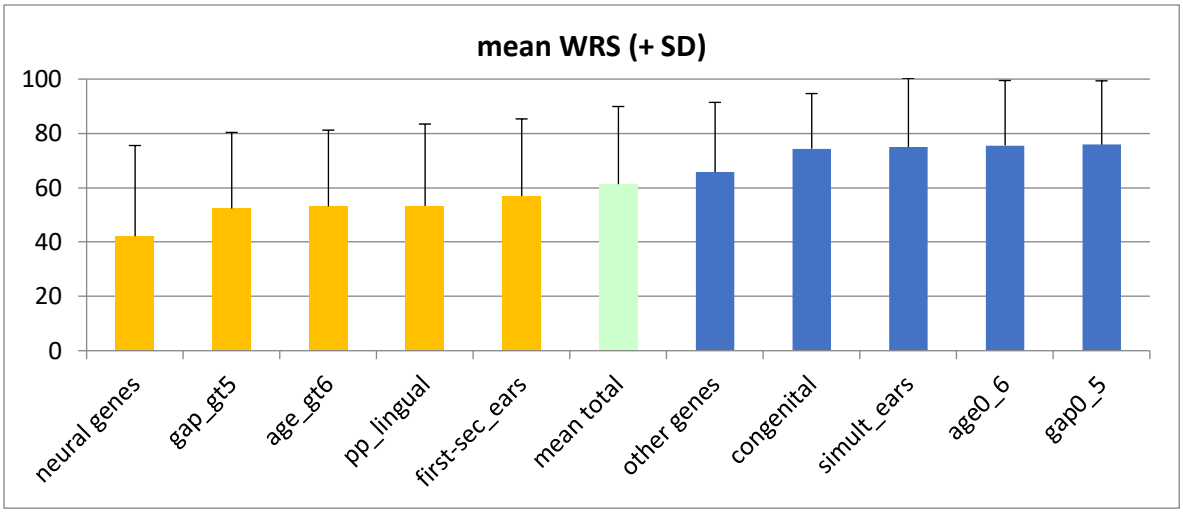

Fig. S5.1. Mean values and SD of WRS_{65} (%) for unfavorable (yellow) and favorable (blue) categories and the total cohort (green).

S5.2 Distributions

Figure S5.2 shows the outcome distributions of the total cohort and of the 10 categories. Inspecting the left column showing the distributions for the WRS_{65}, the outcome parameter investigated so far, all of them show a tendency of skewness, mostly if not always accompanied with outliers. The skewness may be attributed to the nonlinear character of the psychometric curve. We therefore tested whether estimation of the speech-recognition threshold at 50% discrimination (SRT_{50}) leads to less skewed distributions. For the Freiburger speech test, the psychometric curve of the WRS_{65} for normal-hearing subjects is given as a fraction of 1 by

$$WRS = 1/(1 + \exp((L_{50}-L)/s)),$$

where s=25/4.4, L the level at which the test was conducted (i.e., 65 dB SPL), L_{50} the level at which 50% correct response is obtained; cf. e.g. (Kompis et al. 2006). Solving for L_{50}, we obtain what in the following is called speech-recognition threshold (SRT). The transformation of WRS values to SRT leads to undefined values for WRS=0% or 100%, respectively. With 20 words per list for the Freiburger monosyllables test, all WRS values apart from 0 and 100% represent a compartment of 5%, such as 95% representing a compartment of 92.5%-97.5%. We thus set the value of the SRT for 0% and 100% (WRS to the SRT conversion) which is calculated by inserting a "corrected" WRS value of 0.125% and 98.75%, respectively, representing the mean value of the remaining compartment. Of course, the authors are aware that the psychometric curve of normal hearing subjects is not regularly appropriate at high grades of hearing loss, but is considered to be a simple best guess in absence of additional information. The resulting distributions are shown in the right column of Figure S5.2. Indeed, the central part of the distributions, neglecting the outliers, may appear slightly less skewed by visual inspection, and thus more appropriate for an ANOVA. However, testing the 10 distributions with the Kolmogoroff-Smirnov and the Shapiro-Wilk test gave an unequivocal illustration, so we chose to restrict our presentation to statistics of the WRS_{65} outcome.

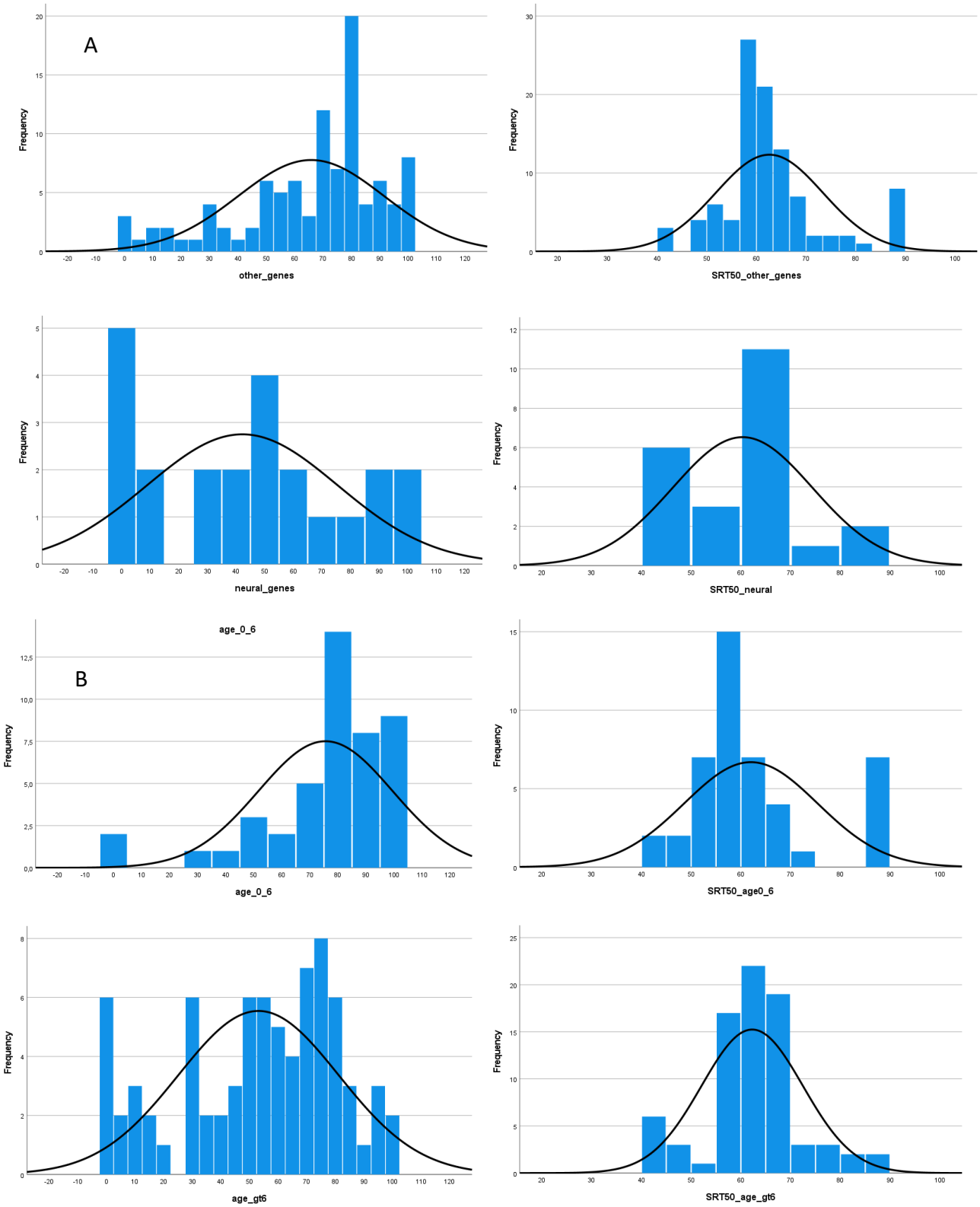

Figure S5.2. Distributions of WRS_{65} for all ten categories, as plotted by SPSS. Favorable categories of one group are shown in the first row of a 2x2 panel, non-favorable in the second row. Distribution of the WRS are shown in the left column, those of SRT in the right column. Distributions of the WRS appear typically to consist of a center region which is not too far from Gaussian shape, but mostly having skewness to the right side, and outliers representing best and poorest performers. The right column shows the correspondent distributions for the SRT50. **Panel A** shows results for the **gene** group, **panel B** for the **age** group.

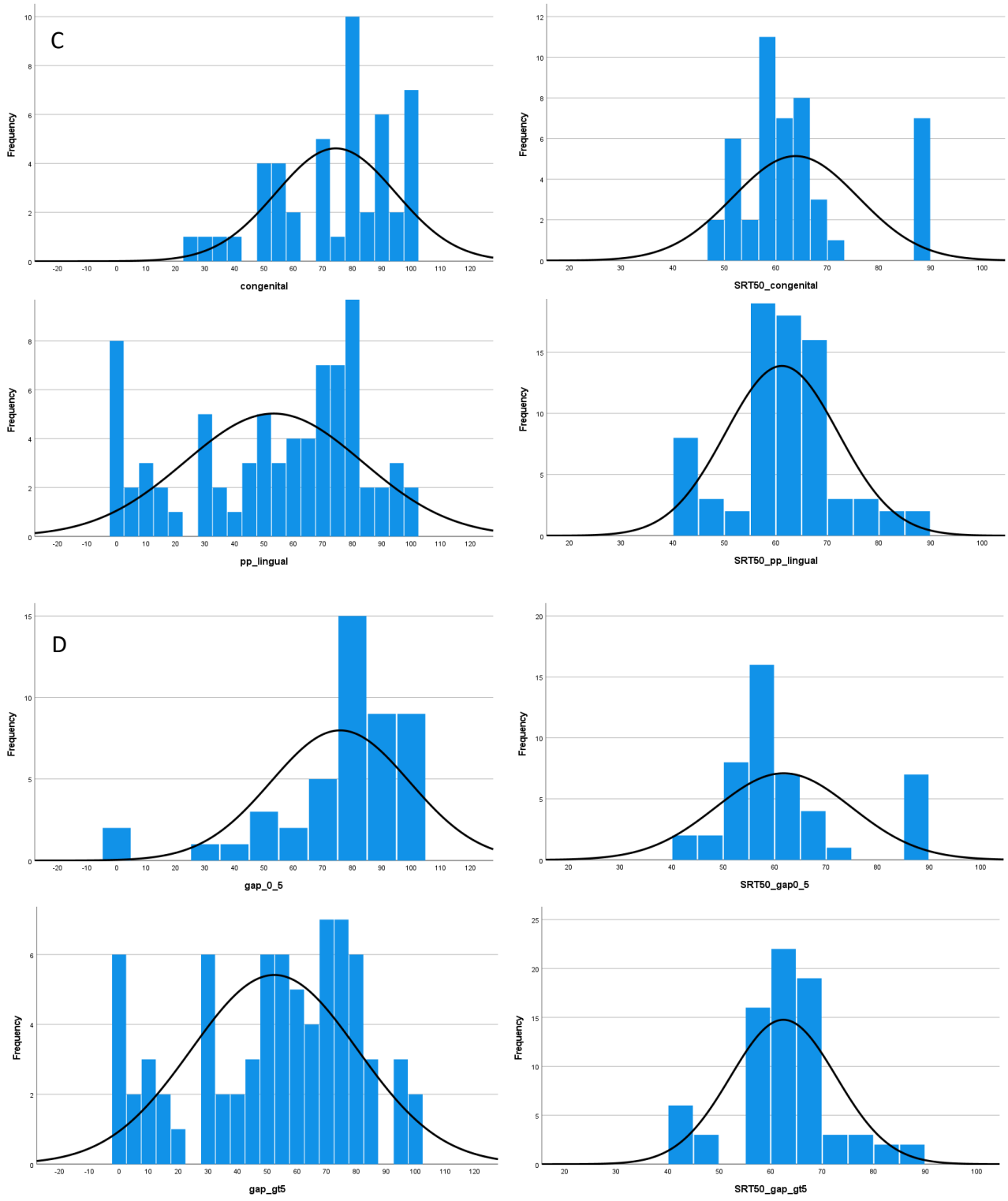

Figure S5.2 (cont'd). **Panel C: Onset** (congenital versus non-congenital; (pre-/peri-/post-lingual)) group. **Panel D: Delay** group (gap between hearing-loss onset and implantation).

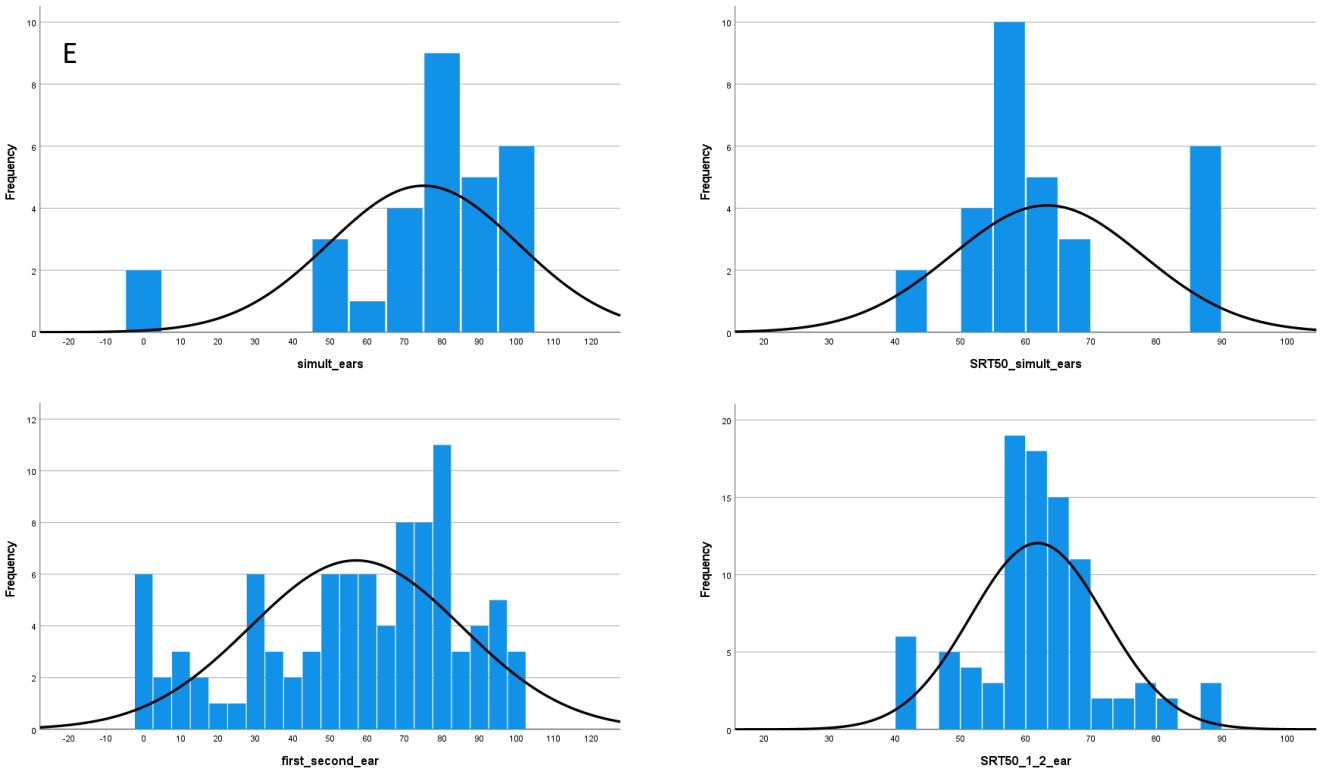

Figure S5.2 (cont'd). **Panel E: Laterality** and implantation order group.

S5.3 Outlier analysis

The 10 categories are obviously not mutually independent. We show in table S5.3 to which categories the outliers, i.e., outperformers and poor performers, belong. For this analysis, outperformers are defined as having 100% WRS in the Freiburger monosyllables test at least in one CI-implanted ear, and poor performers as having 0% WRS at least in one CI-implanted ear. Table S5.2 shows that 5 out of the 6 poorest performers (8 ears) fall into at least 4 of the five non-favorable categories. However, one poor performer belonged only to the non-favorable hearing loss onset category, but otherwise into the favorable categories. This suggests that other relevant factors for poor performance are not included in our analysis. For the best performers, only 5/7 subjects fall predominantly into the favorable categories (3-5). The 2 remaining subjects fell into only 1 or 2 favorable categories.

	gene expression	age at impl. left ear	age at impl. right ear	hear. loss onset (age)	hear. loss onset type	delay HL onset to impl. left ear	delay HL onset to impl. right ear	sequence of implantation
WRS 0%	neural	12		5	pp-ling*	7		1-2-ears
	neural	53	53	35	pp-ling	18	18	1-2-ears
	neural		8	0	cong**		8	1-2-ears
	neural		39	9	pp-ling		30	1-2-ears
	other	51		19	pp-ling	32		1-2-ears
	other	3	3	1	pp-ling	2	2	simult_ears

	gene expression	age at impl. left ear	age at impl. right ear	hear. loss onset (age)	hear. loss onset type	delay HL onset to impl. left ear	delay HL onset to impl. right ear	sequence of implantation.
WRS 100%	other	40	39	10	pp-ling	30	29	simult_ears
	other	38	42	5	pp-ling	33	37	1-2-ears
	neural	2	2	0	cong	2	2	1-2-ears
	other	0	0	0	cong	0	0	simult_ears
	other	0	0	0	cong	0	0	simult_ears
	other	0	0	0	cong	0	0	simult_ears
	other	1	15	0	cong	1	15	1-2-ears

(Numbers given in years. *peri-post-lingual ** congenital)

Table S5.3. **Outlier analysis; Upper part**: 6 poor performers with WRS_{65} of 0% belong mostly to the non-favorable categories (red cells). **Lower part**: 7 outperformers with 100% WRS in at least one ear belong mostly to the favorable categories (blue cells) of the five groups. This is most clearly seen in the first three groups (gene expression/age/hearing loss onset).

S5.4 Statistical post-hoc analysis of cochlear implant outcomes for 10 genetic and demographic categories with n = 76 subjects.

When analyzing 76 subjects instead of 123 ears, we need to adapt the outcome parameter as well as some of the contributing factors in case of bilateral implantation before the analysis can be performed. Thus, in cases of bilateral implantation, the WRS_{65} was computed as the mean value of both ears, and the parameters age at implantation, delay, and (preoperative) hearing loss, were also computed as the mean value before entering the categorization.

The condensation of 30 parameters to 10 resp. five putative factor groups is displayed in Figure S5.4. The distributions are just slightly different compared to Figure 5.1 (main manuscript), due to the change in numbers of ears to patients. The categories contain now 15 to 61 members (Table S5.4).

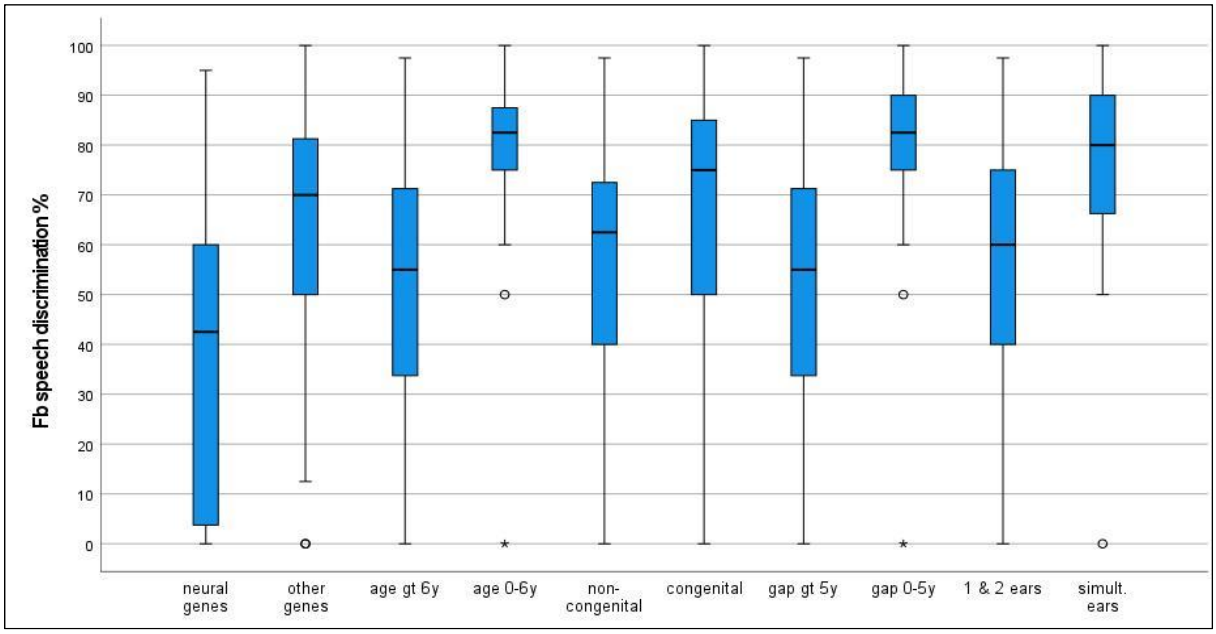

Fig. S5.4.

group	Value Label	N
1	neural genes	16
2	other genes	60
3	age 0-6y	21
4	age gt 6y	55
5	congenital	35
6	non-congenital	41
7	gap 0-5y	21
8	gap gt 5y	55
9	1 & 2 ears	61
10	simult ears	15

Table S5.4: Number of members of the 10 groups for n=76 subjects.

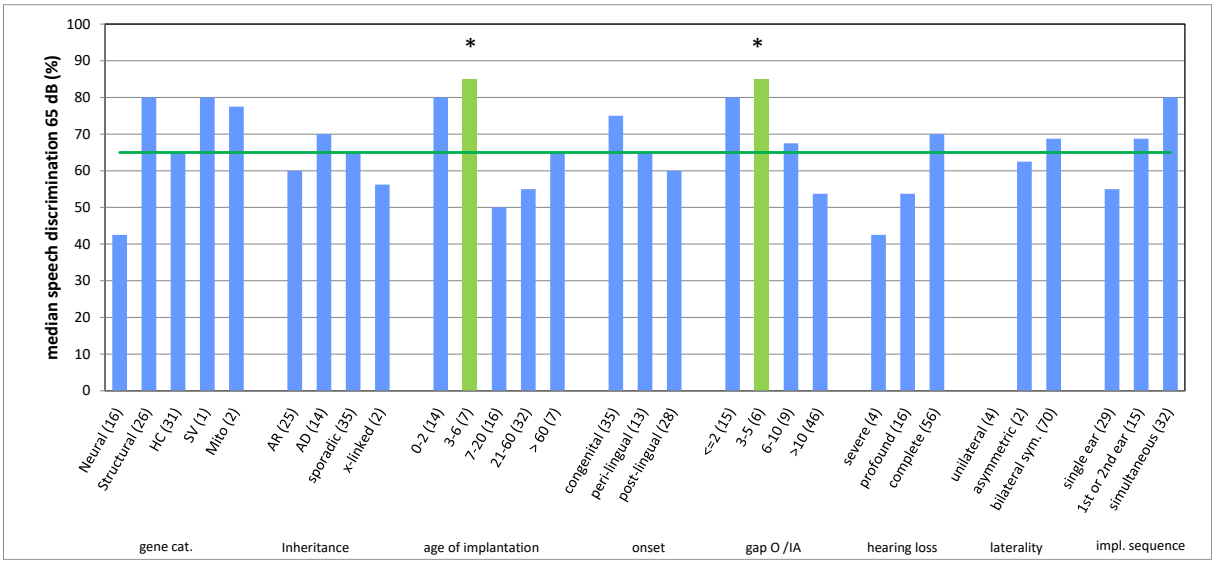

Fig. S5.5 shows the median for the speech discrimination scores when 76 subjects enter the analysis. This figure corresponds to Fig. 5A in the main manuscript where the entries correspond to n=123 ears.

The results for the condensed parameter set are shown in table S5.5.

Parameter Estimates

Dependent Variable:

Parameter	B	Std. Error	t	Sig. p-val.	95% Confidence Interval Lower Bound	Upper Bound	Partial Eta Squared	Noncent. Param.	Observed Power[b]
Intercept	75,000	6,895	10,878	0,000	61,442	88,558	0,242	10,878	1,000
[group=1]	-34,375	9,597	-3,582	**0,000**	-53,246	-15,504	**0,034**	3,582	0,947
[group=2]	-10,667	7,708	-1,384	0,167	-25,824	4,491	0,005	1,384	0,281
[group=3]	2,619	9,027	0,290	0,772	-15,132	20,370	0,000	0,290	0,060
[group=4]	-22,636	7,778	-2,910	**0,004**	-37,931	-7,341	**0,022**	2,910	0,827
[group=5]	-8,786	8,241	-1,066	0,287	-24,990	7,419	0,003	1,066	0,186
[group=6]	-21,524	8,058	-2,671	**0,008**	-37,369	-5,680	**0,019**	2,671	0,759
[group=7]	2,857	9,027	0,317	0,752	-14,894	20,608	0,000	0,317	0,061
[group=8]	-22,727	7,778	-2,922	**0,004**	-38,022	-7,432	**0,023**	2,922	0,830
[group=9]	-19,508	7,696	-2,535	**0,012**	-34,641	-4,375	**0,017**	2,535	0,715
[group=10]	0[a]								

a. This parameter is set to zero because it is redundant.

b. Computed using alpha = .05

Table S5.5. Parameter estimates of the Welch ANOVA for centered data of the 10 categories, as plotted by SPSS. Partial eta values for significant effects are shown in bold and account for 11.5% of the variance. Number of entries: n=76 subjects.

S5.5 Analog statistical analysis for Iowa cohort (Shearer et al, 2017)

When analyzing the data of the Iowa cohort (Shearer et al. 2017) using the same statistical approach with Welch-ANOVA, we confirm that the resultant model with all significant and non-significant parameters accounts for **18.3%** of the variance for all categories. Three of their categories were significant contributors at $p \leq 0.05$, namely bilateral SSNHL (favorable), sensory genetic (favorable), and single-sided deafness (non-favorable), together accounting for **11.6%** of the variance. Neural genes (including patients identified as "neural genetic" by CADD score analysis) accounted for **1.4%** of the variance.

Parameter Estimates

Dependent Variable:

Parameter	B	Std. Error	t	Sig. p-val.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound	**Partial Eta Squared**	Noncent. Parameter	Observed Power[b]
Intercept	-0.112	0.112	-1.003	0.317	-0.333	0.109	0.007	1.003	0.169
Bilateral SSNHL	0.688	0.265	2.601	**0.010**	0.165	1.211	**0.044**	2.601	0.734
Menieres Disease	0.279	0.370	0.753	0.453	-0.453	1.010	0.004	0.753	0.116
Neural - Genetic	-0.305	0.209	-1.461	0.146	-0.718	0.108	0.014	1.461	0.306
Other	-0.480	0.309	-1.553	0.122	-1.091	0.131	0.016	1.553	0.339
Otosclerosis	0.758	0.403	1.883	0.062	-0.037	1.553	0.024	1.883	0.465
Sensory - Genetic	0.633	0.273	2.314	**0.022**	0.092	1.173	**0.035**	2.314	0.633
Single-Sided Deafness	-0.480	0.203	-2.366	**0.019**	-0.882	-0.079	**0.037**	2.366	0.652
Unknown	0[a]								

a. This parameter is set to zero because it is redundant.

b. Computed using alpha = .05

Table S5.3. Parameter estimates of the Welch ANOVA for the 8 categories from Shearer et al., 2017, plotted by SPSS. Parameters significant at the 0.05-level are printed bold.

References

Cohen, J. (1992). A Power Primer. *Psychological Bulletin, 112*, 155-159.

Kompis, M., Krebs, M., Hausler, R. (2006). [Verification of normative values for the Swiss version of the Freiburg speech intelligibility test]. *HNO, 54*, 445-450.

Shearer, A. E., Eppsteiner, R. W., Frees, K., et al. (2017). Genetic variants in the peripheral auditory system significantly affect adult cochlear implant performance. *Hear Res, 348*, 138-142.