DTU Library

A method for calculating the grand average of a set of auditory brain-stem responses

Kristensen, Sinnet G.B.; Elberling, Claus

Published in:
JASA Express Letters

Link to article, DOI:
10.1121/10.0028320

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

Citation (APA):
Kristensen, S. G. B., & Elberling, C. (2024). A method for calculating the grand average of a set of auditory brain-stem responses. *JASA Express Letters*, *4*(9), Article 094405. https://doi.org/10.1121/10.0028320

SEPTEMBER 18 2024

A method for calculating the grand average of a set of auditory brain-stem responses

Sinnet G. B. Kristensen ; Claus Elberling

JASA Express Lett. 4, 094405 (2024)
https://doi.org/10.1121/10.0028320

A method for calculating the grand average of a set of auditory brain-stem responses

Sinnet G. B. Kristensen[1,2,a] and Claus Elberling[3]
[1]Interacoustics Research Unit, c/o: Technical University of Denmark, Kongens Lyngby, DK-2800, Denmark
[2]Hearing Systems, Department of Health Technology, Technical University of Denmark, Kongens Lyngby, DK-2800, Denmark
[3]Geelsskovvej 19, DK-2830 Virum, Denmark
sbkr@iru.interacoustics.com, elberling@privat.dk

Abstract: To calculate a grand average waveform for a set of auditory brain-stem responses (ABRs), no generally accepted method exists. Here, we evaluate a new method using temporal adjustment of the underlying ABRs. Compared to a method without temporal adjustment, the new method results in higher amplitudes of the individual waves in the grand average. The grand average produced by the method better represents the group mean wave-amplitudes because it reduces smearing of the individual waves caused by inter-subject latency variability.

[Editor: Qian-Jie Fu] https://doi.org/10.1121/10.0028320

Received: 23 April 2024 **Accepted:** 3 August 2024 **Published Online:** 18 September 2024

1. Introduction

When recording evoked potentials from a homogeneous group of subjects under the same conditions, the calculation of a grand average (GA) or a grand mean waveform has been a common choice of analysis and presentation. Separate GA waveforms have then been used to demonstrate different waveform morphology among conditions or subject groups (Boutros *et al.*, 1993; Giard *et al.*, 1994; Polonenko and Maddox, 2019; Woods, 1995). GA waveforms have also been used as templates to verify modeling outcome (Kerr *et al.*, 2008; Rønne, 2012). However, no consensus exists with regard to a procedure of calculating the GA that respects multiple waveform morphology features. This is highly apparent in the auditory brain-stem response (ABR) where the complete waveform morphology consists of multiple peaks with different latencies. The GA method used most often for ABR is to calculate the simple average of the ABRs, with no temporal adjustment of the individual recordings. Therefore, the GA waveform will encounter smearing, due to the naturally occurring inter-subject variability of the latencies of the dominant peaks of the ABR (e.g., Elberling and Parbo, 1987). Picton *et al.* (1988) introduced dynamic time warping to evaluate brain-stem auditory evoked potentials and to create a template or GA of a set of recorded ABRs. The method was implemented as an automatic procedure, using the values of all sample points within a temporal window of each recording to calculate the temporal characteristics for the time warping. The method does not incorporate visual identification of the dominant waves of the ABR and, therefore, introduced some amplitude errors.

In recent publications, a temporal adjustment of the wave V of all underlying waveforms to the mean wave V latency of the group before making the GA, has been used (Cebulla and Elberling, 2010; Elberling and Don, 2008; Elberling *et al.*, 2010, 2012; Kristensen and Elberling, 2012). This procedure results in a well-represented wave V morphology, but due to inter-subject variability in, for example, the wave I-V interval, the negative consequence of this procedure is a smearing of the remaining peaks in the GA waveform. This was highlighted in Kristensen and Elberling (2012, their Fig. 6), where, in one condition, wave I was used for the temporal adjustment instead of wave V. This resulted in a much larger wave I amplitude with a more prominent wave I peak and trough. The method we have used to generate GAs in our previous publications is not optimal, since we only embrace one wave at a time (wave I or V), especially if the GA waveform characteristics deviate significantly from the group mean amplitude or typical waveform morphology.

To compensate for the shortcoming of current GA procedures' ability to correctly represent the prominent waves (peaks and troughs) in the same GA waveform, we hereby suggest a new principle for an underlying temporal adjustment. For a group of ABRs, the principle is to time shift (forwards or backwards) the prominent waves of each recording so their timing coincides with a set of reference values corresponding to the group mean latencies. At the outset, each prominent wave is identified visually.

[a]Author to whom correspondence should be addressed.

2. Methods

2.1 Principle of temporal adjustment

The principle of the temporal adjustment is for each ABR to compress (or expand) the time-axis such that the latency of each prominent wave (here: peak I, III, and V and the corresponding troughs) coincides with a reference value, corresponding to the group mean latency. The principle of the suggested method, which is inspired by Picton *et al.* (1988), is sketched in Fig. 1. The reference values are plotted along the x axis, and a sketched ABR is shown along the y axis. This example uses reference values corresponding to the group mean latency values for wave I, III, V, and V′ (the trough following wave V). The temporal deviations between the latencies of the sketched ABR (along the y axis) and the reference values (along the x axis) indicate the necessary temporal adjustments. After the adjustments, the points for the individual waves are shifted up or down in order to coincide with the diagonal line (gray line). No temporal adjustments are made for the 0 and 10 ms end points. The temporal adjustments between the prominent waves are derived by linear interpolation as indicated by the straight lines (here five lines). These lines can easily be described mathematically and subsequently used to compute the temporal adjustment, τ, for each sample point of the sketched ABR within the chosen temporal window (10 ms). As an example, the slope, α, of the straight line between peak V and the following trough V′, and the corresponding temporal adjustment, τ, are given below:

$$\alpha = (t_{V'} - t_V)/(t_{V'ref} - t_{Vref}), \quad (1)$$

$$\tau = (1/\alpha - 1) \cdot t - 1/\alpha \cdot t_V + t_{Vref}. \quad (2)$$

This formula [Eq. (2)] gives the temporal adjustment for each time point, t, of the sketched ABR between and including wave V and V′. A negative value of τ means that the time variable, t, should be reduced (shifted downwards in Fig. 1), corresponding to temporal compression, while a positive value of τ means that t should be enlarged (shifted upwards in Fig. 1), corresponding to temporal expansion.

Using the values (shown in Fig. 1), $t_V = 6.27$, $t_{V'} = 7.33$, $t_{Vref} = 5.43$, and $t_{V'ref} = 6.35$ ms, the corresponding slope and formula for the temporal adjustment can be calculated:

$$\alpha = (7.33 - 6.27)/(6.35 - 5.43) = 1.152, \quad (3)$$

$$\tau = (1/1.152 - 1) \cdot t - 1/1.152 \cdot 6.27 + 5.43 \quad \text{or} \quad \tau = -0.132 \cdot t - 0.012. \quad (4)$$

For the sketched ABR in Fig. 1, the temporal sections around wave III, V, and V′ should be compressed, while the section around wave I should be expanded.

2.2 Subjects

Different GA versions were evaluated on ABRs recorded in 20 normal-hearing adults (12 males, 8 females) ranging from 21 to 36 years of age (median age 25 years). All participants had pure-tone thresholds ≤15 dB HL for the frequencies from

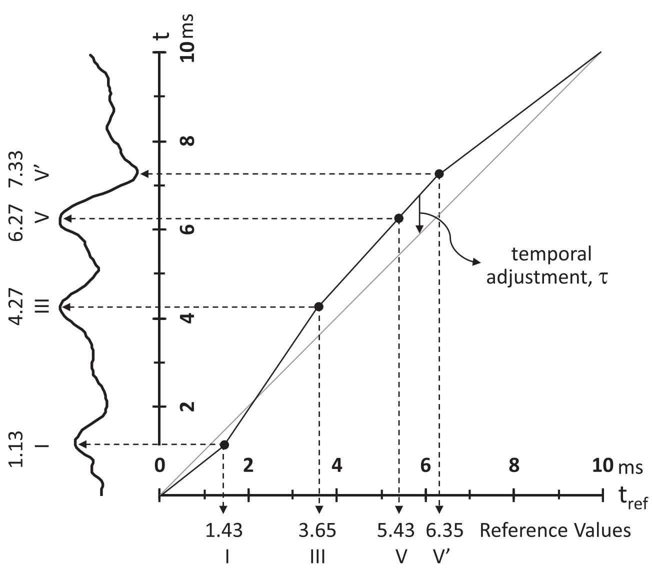

Fig. 1. Principle of the temporal adjustment shown for a sketched ABR. The reference values (group mean latencies) for wave I, III, V, and V′ are plotted along the x axis, t_{ref}, and the sketched ABR along the y axis, t, (See text for further details.)

125 to 8000 Hz. One ear was tested on each participant, with a balanced left and right ear occurrence. Otoscopy was performed to ensure no wax obstruction and ear canals suitable for placement of the insert earphone.

2.3 ABR recording and analysis

The ABRs were recorded using the Interacoustics Eclipse EP25 ABR system. The subjects were placed on a bed in an electrically shielded test booth and instructed to relax and sleep if possible. The EEG signal was picked up between the electrodes on the mid-frontal area (F_z) and the ipsilateral mastoid (M_1). An electrode on the cheek served as ground. The EEG signal was bandpass filtered from 100 Hz to 3 kHz (12 dB/octave) with an EEG artifact rejection level of $\pm 40\,\mu$V. Weighted averaging was applied (Elberling and Wahlgreen, 1985), and a running estimate of background noise was made (Elberling and Don, 1984). A residual background noise of <30 nV (Don and Elberling, 1994) and a minimum of 4500 accepted sweeps were used as a dual stop criterion. A standard 100 μs Click stimulus (300–10 000 Hz) was used to evoke individual ABRs. The stimulus was presented at 80 dB nHL via ER-3A insert earphones (Ear-Tone ABR insert phones), acoustically calibrated in dB nHL in the occluded-ear simulator specified in IEC 60318-4 (2010) and using the reference value (RETSPL in dB p-p.e.SPL) published by ISO 389-6 (2007). The Click stimulus was presented with alternating polarity and at a rate of 27.1 stimuli/s.

The 20 ABRs were visually inspected, and all waveforms demonstrated a clear wave I, III, and V as well as the corresponding troughs I′, III′, and V′. The peak latencies and peak-to-peak amplitudes of all three wave peaks were measured and used to calculate the group mean values and their standard deviations (see Table 1).

With the described method, the following seven GA waveforms were calculated: (1) no adjustment (GA_{norm}), (2) adjustment of wave I (GA_I), (3) adjustment of wave V (GA_V), (4) adjustment of wave I and V ($GA_{I\ V}$), (5) adjustment of wave I, III, and V ($GA_{I\ III\ V}$), (6) adjustment of wave I, III, V, and V′ ($GA_{I\ III\ V\text{-}V'}$), and (7) adjustment of wave I, I′, III, III′, V, and V′ ($GA_{I\text{-}I'\ III\text{-}III'\ V\text{-}V'}$).

3. Results

Figure 2 shows three of the GA waveforms: one with no temporal adjustment of the underlying ABRs (GA_{norm}), one with adjustment of wave V (GA_V), and one with adjustment of all the peaks and throughs ($GA_{I\text{-}I'\ III\text{-}III'\ V\text{-}V'}$).

To explore how well each GA version is representing the individual ABR, the correlation coefficient, R (using the time window 0–8 ms) was calculated between each temporally adjusted ABR and the corresponding GA. The group mean R value for each GA version is shown in Table 1. For GA_{norm}, a correlation coefficient of $R = 0.87$ is obtained, but it becomes significantly larger when the GA method adjusts for the wave V latency ($R = 0.92$, $p < 0.01$) and reaches its maximum value ($R = 0.94$, $p < 0.01$) when also the wave V′ latency is included in the adjustment. The percentage of the mean wave I, III, and V amplitude that was obtained by each GA method was calculated and shown in Table 1. The results demonstrate that GA_{norm} performs the poorest by only being able to obtain 86% of the mean wave I amplitude,

Table 1. Wave I, III, and V: Mean and standard deviation of wave I, III, and V latency and amplitude across the individual recordings (N = 20), and wave I, III, and V amplitude in the seven different GAs (both as absolute values in [nV] and in [%] of the corresponding group mean value). The table shows both the amplitude of the GAs and their significance (one-tailed *t* test). The significance indicates whether the amplitude of the GA deviates significantly from the corresponding group mean value (NS, non-significant at the 5% level). The Pearson correlation, R, was calculated between each time-adjusted recording and the corresponding GA over an 8 ms time window. The table shows both the mean R values and their significance (one-tailed paired *t* test). The significance indicates whether the mean R value for the GAs deviates significantly from the value for GA_{norm} (NS, non-significant at the 5% level). Both the mean values and their significance are calculated via Fischer's Z-transform).

	Wave I				Wave III				Wave V				Correlation coefficient	
	Mean	SD	%	Significance	Mean	SD	%	Significance	Mean	SD	%	Significance	Mean	Significance
Individual recordings (N = 20)														
Latency (ms)	1.43	0.105	—	—	3.65	0.190	—	—	5.43	0.216	—	—	—	—
Amplitude (nV)	240	105	—	—	256	121	—	—	566	115	—	—	—	—
GA														
Amplitude (nV)														
GA_{norm}	207	—	86	NS	181	—	71	$p < 0.01$	478	—	85	$p < 0.01$	0.87	—
GA_I	228	—	95	NS	189	—	74	$p < 0.05$	476	—	84	$p < 0.01$	0.88	NS
GA_V	219	—	91	NS	203	—	79	$p < 0.05$	539	—	95	NS	0.92	$p < 0.01$
$GA_{I\ V}$	229	—	95	NS	197	—	77	$p < 0.05$	539	—	95	NS	0.92	$p < 0.01$
$GA_{I\ III\ V}$	231	—	96	NS	245	—	96	NS	539	—	95	NS	0.93	$p < 0.01$
$GA_{I\ III\ V\text{-}V'}$	231	—	96	NS	245	—	96	NS	566	—	100	NS	0.94	$p < 0.01$
$GA_{I\text{-}I'\ III\text{-}III'\ V\text{-}V'}$	240	—	100	NS	256	—	100	NS	566	—	100	NS	0.94	$p < 0.01$

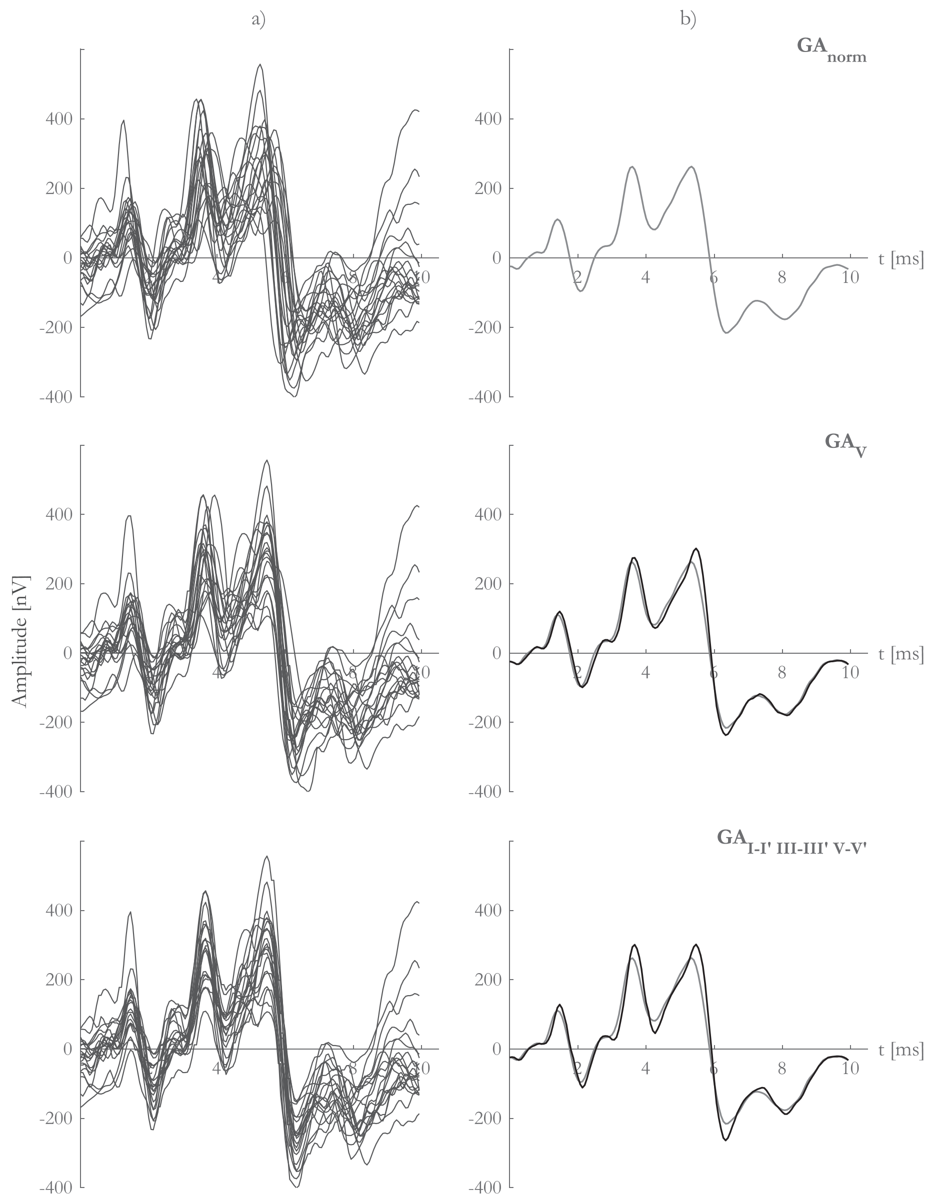

Fig. 2. On the right side (b) GA waveforms are presented based on either no temporal adjustment of the underlying ABRs (GA_{norm}), temporal adjustment only of wave peak V (GA_V), or temporal adjustment of all the peaks and throughs: I, I′, III, III′, V, and V′ ($GA_{I\text{-}I'\ III\text{-}III'\ V\text{-}V'}$), with the GA_{norm} displayed for reference (gray line). The left side (a) displays all 20 corresponding ABR waveforms and their respective placement for each GA method.

71% of the mean wave III amplitude, and 85% of the mean wave V amplitude. When all three wave peak latencies are temporally adjusted, the numbers are as follows: wave I, 96%; wave III, 96%; and wave V, 95%. When all six reference values are used, i.e., the temporal adjustment also includes the three troughs, the group mean amplitude of all three wave peaks is, of course, represented correctly in the GA ($GA_{I\text{-}I'\ III\text{-}III'\ V\text{-}V'}$).

4. Discussion and Conclusion

GA waveforms are commonly used for templates to express common morphological characteristics for a subject group and/or a specific recording condition. The results presented here highlight the advantage of using a method that accurately represents the underlying individual waveforms in the GA. When the wave V latency is included in the temporal adjustment, the mean correlation ($R = 0.92$) becomes significantly higher than for GA_{norm} ($R = 0.87$). This finding is expected because in a classical ABR waveform it is the wave V complex that dominates the correlation coefficient (e.g., Elberling, 1979).

The results show that, when the temporal adjustment of the ABRs includes several wave peaks (and/or troughs), the accuracy of the GA is further enhanced. In cases where only wave V can be identified (for instance, at a lower stimulus level), the results also indicate that the underlying ABRs are better represented in the GA by adjusting to wave V latency, than not applying any adjustment at all. In the analysis of ABRs, the absolute wave V latency is most often evaluated, whereby the information required to make a simple temporal adjustment is readily available. This can easily be performed either with the method suggested here (i.e., non-linear temporal adjustment of each ABR keeping the end-points fixed) or with a temporal shifting of the individual recording (i.e., all data points of each ABR shifted with the same amount), which makes the wave V latency correspond to the group mean value (e.g., Elberling and Don, 2008).

The method by Picton *et al.* (1988) appears to be relatively complex, but it results in a template (or GA) with much the same improvements over a normal averaged template, as we have found for our method herein. However, the wave V amplitude of the GA by Picton *et al.* (1988) was, surprisingly, larger than the group mean value. This may be due to how the V′ trough is identified, or as Picton *et al.* (1988) explains: "*….we found that this was due to the warping procedure occasionally bringing into the V′ position a part of the wave form that was more than 3 msec later than wave V*" (p. 219). This demonstrates the importance of an accurate identification of each prominent ABR wave (peak or trough).

Despite the relatively constant interpeak interval, it is known that a biological sex difference exists, with, for instance, males having larger wave I-V intervals than females (e.g., Elberling and Parbo, 1987). When deciding to evaluate data from a mixed-biological sex population, temporal adjustment of the underlying ABRs will provide a less smeared GA, as its nature can take this difference into account.

The present study suggests applying a temporal adjustment of the underlying ABRs to reduce GA waveform smearing caused by inter-subject latency variability. This results in a GA waveform that can account for multiple waveform morphology features. The different GAs compared here highlight the importance of using as many reference values as available (for all individual ABRs in the group) when presenting data in a GA format. In contrast to GA_{norm}, $GA_{I\text{-}I'\ III\text{-}III'\ V\text{-}V'}$ relies on the latencies of a total of six peaks and troughs which, in this study, could be measured accurately in all the individual ABRs.

This, however, will only be possible at higher stimulation levels and when a sufficient recording quality (signal-to-noise ratio) can be obtained. Spurious peaks in the residual background noise will not only influence the precision of the measured latencies but also the measured peak-to-peak amplitudes (Don and Elberling, 1996). A poor recording quality might affect the temporal adjustment method, and align peaks of the noise instead of peaks of the true (noise-free) ABR. An increasing noise level will therefore degrade the adjustment method; on the other hand, there is hardly any meaning in creating a GA based on low-quality recordings. As a corollary of the specifications for recording the 20 ABRs used herein, the residual background noise of all the GAs is $<6.7\ nV_{RMS}$ ($30\ nV_{RMS}/\sqrt{20}$).

Acknowledgments

This project was supported in part by Innovations Fund Denmark Grant No. 9065-00094B.

Author Declarations

Conflict of Interest

S.G.B.K. is employed at Interacoustics A/S. S.G.B.K. and C.E. are shareholders in Demant A/S.

Ethics Approval

The experimental work was carried out under ethical approval from the Science-Ethic Committee for the Capital region of Denmark (H-1–2013-138), and a consent form was signed by all participants.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Boutros, N., Zouridakis, G., Rustin, T., Peabody, C., and Warner, D. (**1993**). "The P50 component of the auditory evoked potential and subtypes of schizophrenia," Psychiatry Res. **47**(3), 243–254.

Cebulla, M., and Elberling, C. (**2010**). "Auditory brain stem responses evoked by different chirps based on different delay models," J. Am. Acad. Audiol. **21**(7), 452–460.

Don, M., and Elberling, C. (**1994**). "Evaluating residual background noise in human auditory brain-stem responses," J. Acoust. Soc. Am. **96**(5), 2746–2757.

Don, M., and Elberling, C. (**1996**). "Use of quantitative measures of auditory brain-stem response peak amplitude and residual background noise in the decision to stop averaging," J. Acoust. Soc. Am. **99**(1), 491–499.

Elberling, C. (**1979**). "The use of templates and cross correlation functions in the analysis of brain stem potentials," Scand. Audiol. **8**, 187–190.

Elberling, C., Callø, J., and Don, M. (**2010**). "Evaluating auditory brainstem responses to different chirp stimuli at three levels of stimulation," J. Acoust. Soc. Am. **128**(1), 215–223.

Elberling, C., and Don, M. (**1984**). "Quality estimation of averaged auditory brainstem responses," Scand. Audiol. **13**(3), 187–197.
Elberling, C., and Don, M. (**2008**). "Auditory brainstem responses to a chirp stimulus designed from derived-band latencies in normal-hearing subjects," J. Acoust. Soc. Am. **124**(5), 3022–3037.
Elberling, C., Kristensen, S. G., and Don, M. (**2012**). "Auditory brainstem responses to chirps delivered by different insert earphones," J. Acoust. Soc. Am. **131**(3), 2091–2100.
Elberling, C., and Parbo, J. (**1987**). "Reference data for ABRs in the retrocochlear diagnosis," Scand. Audiol. **16**, 49–55.
Elberling, C., and Wahlgreen, O. (**1985**). "Estimation of auditory brainstem response, ABR, by means of Bayesian inference," Scand. Audiol. **14**(2), 89–96.
Giard, M. H., Perrin, F., Echallier, J. F., Thévenet, M., Froment, J. C., and Pernier, J. (**1994**). "Dissociation of temporal and frontal components in the human auditory N1 wave: A scalp current density and dipole model analysis," Electroencephalogr. Clin. Neurophysiol. **92**(3), 238–252.
IEC 60318-4 (**2010**). *Electroacoustics—Simulators of Human Head and Ear—Part 4: Occluded-Ear Simulator for the Measurement of Earphones Coupled to the Ear by Means of Ear Inserts* (International Electrotechnical Commission, Geneva, Switzerland).
ISO 389-6 (**2007**). "Acoustics—Reference zero for the calibration of audiometric equipment—Part 6: Reference threshold of hearing for test signals of short duration" (International Organization for Standardization, Geneva, Switzerland).
Kerr, C. C., Rennie, C. J., and Robinson, P. A. (**2008**). "Physiology-based modeling of cortical auditory evoked potentials," Biol. Cybern. **98**(2), 171–184.
Kristensen, S. G. B., and Elberling, C. (**2012**). "Auditory brainstem responses to level-specific chirps in normal-hearing adults," J. Am. Acad. Audiol. **23**(9), 712–721.
Picton, T., Hunt, M., Mowrey, R., Rodriguez, R., and Maru, J. (**1988**). "Evaluation of brain-stem auditory evoked potentials using dynamic time warping," Electroencephalogr. Clin. Neurophysiol. **71**, 212–225.
Polonenko, M. J., and Maddox, R. K. (**2019**). "The parallel auditory brainstem response," Trends Hear. **23**, 1–17.
Rønne, F. M. (**2012**). "Modeling auditory evoked potentials to complex stimuli," Ph.D. thesis, Technical University of Denmark, Kongens Lyngby, Denmark.
Woods, D. L. (**1995**). "The component structure of the N1 wave of the human auditory evoked potential," Electroencephalogr. Clin. Neurophysiol. Suppl. **44**, 102–109.