Use of Electrically Evoked Compound Action Potentials for Cochlear Implant Fitting: A Systematic Review

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Objectives: The electrically evoked compound action potential (eCAP) is widely used in the clinic as an objective measure to assess cochlear implant functionality. During the past decade, there has been increasing interest in applying eCAPs for fitting of cochlear implants. Several studies have shown that eCAP-based fitting can potentially replace time-consuming behavioral fitting procedures, especially in young children. However, a closer look to all available literature revealed that there is no clear consensus on the validity of this fitting procedure. This study evaluated the validity of eCAP-based fitting of cochlear implant recipients based on a systematic review of the recent literature.

Design: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses were used to search the PubMed, Web of Science, and Cochrane Library databases. The term "eCAP" was combined with "cochlear implants," "thresholds," and "levels," in addition to a range of related terms. Finally, 32 studies met the inclusion criteria. These studies were evaluated on the risk of bias and, when possible, compared by meta-analysis.

Results: Almost all assessed studies suffered from some form of risk of bias. Twenty-nine of the studies based their conclusion on a group correlation instead of individual subject correlations (analytical bias); 14 studies were unclear about randomization or blinding (outcome assessment bias); 9 studies provided no clear description of the populations used, for example, prelingually or postlingually implanted subjects (selection bias); and 4 studies had a high rate of loss (>10%) for patients or electrodes (attrition bias). Meta-analysis of these studies revealed a weak pooled correlation between eCAP thresholds and both behavioral T- and C-levels (r = 0.58 and r = 0.61, respectively).

Conclusions: This review shows that the majority of the assessed studies suffered from substantial shortcomings in study design and statistical analysis. Meta-analysis showed that there is only weak evidence to support the use of eCAP data for cochlear implant fitting purposes; eCAP thresholds are an equally weak predictor for both T- and C-levels. Based on this review, it can be concluded that research on eCAP-based fitting needs a profound reflection on study design and analysis to draw well-grounded conclusions about the validity of eCAP-based fitting of cochlear implant recipients.

Key words: Cochlear implant, eCAP, Electrically evoked compound action potential, Fitting, Level, Meta-analysis, Threshold.

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INTRODUCTION

A cochlear implant (CI) is a device that can partially restore hearing in patients who are profoundly deaf or severely hard of hearing. To successfully restore speech perception, the settings of the CI must be optimized for the individual patient, called fitting. When fitting a CI, the behavioral threshold (T) and maximum comfortable hearing levels (C-level/M-level/MCL, terminology varies depending on manufacturer) for each electrode contact of the electrode array are set. In this review, these levels will be denoted as T- and C-levels, respectively. Because of intracochlear changes (e.g., intracochlear fibrosis) and patient adaptation to the implant, the T- and C-levels are prone to change during the first few months after implantation (Hughes et al. 2001), or gradually throughout the life cycle of an implant (Smoorenburg et al. 2002). Therefore, it is necessary to fit the CI periodically. CI fitting is often a time-consuming process, which preferably is conducted by an experienced audiologist. Vaerenberg et al. (2014) showed that the applied fitting method differs between CI centers and even between audiologists; there is no golden standard for fitting CIs. The actual fitting profile is a product of both the audiologist and the CI patient, whereby the patient must respond to presented stimuli. However, not all CI recipients can respond adequately, especially young children, elderly (e.g., due to cognitive decline) and mentally challenged patients. Consequently, the fit may be suboptimal, resulting in possibly limited speech recognition or a delay in language development in children (Caner et al. 2007).

Since the advent of modern CIs with telemetry function, clinical research has focused on the use of the electrically evoked compound action potential (eCAP) for fitting as an additive or alternative to behavioral fitting (Brown et al. 2000). The eCAP represents the neural response of spiral ganglion cells lining the inner part of the cochlea (Rosenthal's channel) and can be measured in response to electrical stimulation by the telemetry function of a CI. Although all CIs measure the same electrophysiological response, each CI manufacturer has its own measurement method and terminology to depict the measurement of these neural responses: Neural Response Telemetry (NRT) by Cochlear (Sydney, Australia), Neural Response Imaging (NRI) by Advanced Bionics (Valencia, CA), and Auditory Response Telemetry (ART) by MED-EL (Innsbruck, Austria). As all terms denote the same principle, the general term eCAP will be used throughout the paper for this type of measurement. To enable the use of eCAP in clinical practice, CI manufacturers embedded eCAP measurement features in the fitting software. Especially the latest generation fitting software, for example, Custom Sound (Cochlear), Soundwave (Advanced Bionics), and Maestro (MED-EL), have made the use of objective data to obtain direct baseline fitting maps easily accessible. In parallel with this development, objective fitting of CIs has become of more interest; the feasibility of this approach has been studied extensively in the last decades, however, with contradictory results.

The aim of this systematic review was to assess whether eCAPs can be used for CI fitting purposes. Relevant literature was analyzed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method (Rosenfeld 2010). The studies were assessed on both study design and statistical methodology. Our analyses revealed that the quality of the various studies differs largely and that some conclusions are based on incorrect analysis methods. It is of main importance that the conclusion of most papers about objective fitting is not representative for the individual subjects. In the literature we reviewed, the correlation between eCAP and behavioral thresholds was mostly analyzed using grouped data, while the correlation within individuals is essential to investigate eCAP-based fitting; the group correlation can be qualitatively different from the within-subject association. To clarify, due to the intersubject variability, individual correlations disappear when the individual threshold values are combined in a grouped data set. This phenomenon, which is better known as Simpsons' Paradox (Julious & Mullee 1994), could lead to an analytical bias. This review will show that the prevention of this bias is of great importance in the research of eCAP thresholds.

METHODS

Literature Selection

To ensure that the review included all relevant literature, the initial search included terms encompassing all suitable objective neural response measurements ("eCAP," electrically evoked stapedius reflex threshold, and electrically evoked auditory brainstem response). These terms were combined with "CIs," "thresholds," and "levels," and extended with a range of related terms to include all relevant literature. We searched for papers published from 1995 to June 22, 2015. The search strategy (see Appendix 1 – Literature search in Supplemental Digital Content 1, http://links.lww.com/EANDH/A368) was developed in cooperation with a trained librarian at Leiden University Medical Centre. The PubMed, Web of Science, and Cochrane Library databases were searched at June 22 and 26, 2015. From these papers, all studies concerning eCAPs were manually selected for final analysis using the PRISMA guidelines to minimize publication bias and improve reproducibility.

Consecutively, all papers were screened based on title and abstract to determine whether they met the inclusion criteria: English, Dutch, or German language; measurements conducted in humans; comparison of eCAP and T/C-levels; and the use of Pearson's correlation coefficient for the analysis. We screened on the most commonly used Pearson's correlation coefficient, because a uniform correlation coefficient was required for proper meta-analysis. Furthermore, the inclusion criteria were applied regardless of study quality, because the quality of the study was assessed in a later stage of the review. Papers from the same author were checked for an overlap of study participants. When two papers used identical populations and similar measurement techniques, the papers were treated as one study. When one of the papers was written based on preliminary data and the follow-up study data were available in the second paper, only the final data were used.

Risk of Bias Assessment

The study quality was assessed using a risk of bias (ROB) assessment. All included papers were assessed on four types of bias relevant in their field of research: attrition bias, selection bias, outcome assessment bias, and analytical bias (Table 1).

TABLE 1. Overview of the test conditions to score the different risks of bias

Design Characteristic	Test Condition
Attrition bias	Is the loss to follow-up higher than 10%?
Selection bias	Are eligible patients not representative for the population intended to be analyzed?
Outcome assessment bias	Are the researchers not blinded or comparing linked measurements?
Analytical bias	Are the data not analyzed appropriately for answering the research question?

Attrition Bias • This describes the loss of study participants during follow-up. The ROB was considered high for studies with >10% loss to follow-up (Dumville et al. 2006). We encountered some studies that excluded poor eCAP responders, while other studies considered them as attrition. To be consistent, poor eCAP responders were treated as excluded subjects in this review and not scored as attrition.

Selection Bias • This is the selection of data in such a way that it is not representative of the population intended to be analyzed. To prevent selection bias, the subjects should be selected on predefined selection criteria in accordance with the research question. Moreover, the subject must be selected randomly. For example, CI recipients are a heterogenic group consisting of prelingually and postlingually deaf subjects with large variation in age of implantation and duration of hearing loss. Depending on these factors, language development and overall performance can differ during fitting (Petersen et al. 2013). When eligible patients were randomly selected from the intended population the risk of selection bias was low.

Outcome Assessment Bias • This is an error made by comparing two measurements which are not independent, or are linked to each other. The following cases were scored as being at risk for outcome assessment bias: (1) when eCAP threshold profiles were adjusted to T- or C-levels using behavioral information, for example, as applied by Willeboer and Smoorenburg (2006); and (2) when the objective and behavioral measurements are performed by the same person, whereby the knowledge of objective performance can severely influence the results of behavioral measurements.

Analytical Bias • This is an error introduced when data are not analyzed appropriately for answering the research question. For example, when answering the question whether eCAP thresholds could be used to predict fitting levels, correlation analysis of eCAP threshold with T- and C-levels (hereafter denoted as T-eCAP and C-eCAP, respectively) should be performed at the level of individual subjects and not for the population as a whole.

Meta-Analysis

A meta-analysis was performed on the studies that provided Pearson's correlation coefficient for T-eCAP or C-eCAP analysis. The analysis was performed in the R software environment (Free Software Foundation's GNU General Public License, version 2.18). The T-eCAP and C-eCAP correlations of each study were pooled to estimate their overall correlation and associated confidence interval (c.i.). For studies showing the correlation coefficients of individual patients (Franck & Norton 2001; Franck 2002; Potts et al. 2007; Holstad et al. 2009), the mean of the individual

correlations for T-eCAP and C-eCAP was used as study-specific correlation. The study-specific correlations were transformed by using Fisher's *r*-to-z transformation (Hedges & Olkin 1985) and, subsequently, a weighted pooled correlation of these transformed scores has been computed (Borenstein 2009). For both T-eCAP and C-eCAP, a fixed and random effects model was estimated. The fixed model assumes that the variation between study results is due to chance alone. The random model also takes into account between study differences, for example, sample size. Additionally, an overall measure of heterogeneity between studies was reported, whereby the I^2 shows the percentage of variance attributable to study heterogeneity and τ^2 is an estimate of the between-study variance in the random effects model (DerSimonian & Laird 1986). A sensitivity analysis was performed to investigate the robustness of the meta-analysis by looking how the results are affected by different types of studies. The tested groups were: studies based on group correlations (n = 11), studies based on individual correlations (n = 3), studies with adequate blinding (n = 10), studies with adults only (n = 6), and studies with children only (n = 2).

RESULTS

Overview of Selected Literature

Figure 1 shows the flow diagram of our PRISMA analysis. The search strategy provided 1972 papers, 1515 after removing duplicates. A total of 160 papers met our inclusion criteria as defined in the methods section. Assessing the papers for eligibility provided 68 items, 37 of which used eCAP as objective measure (others were electrically evoked stapedius reflex threshold and electrically evoked auditory brainstem response). These 37 papers were finally included in the review (see Table 2 for references). Papers from the same author were checked for an overlap of study participants. Ten papers were combined into five studies: Franck and Norton (2001) with Franck (2002); Thai-Van et al. (2001) with Thai-Van et al. (2004); Akin et al. (2006) with Akin et al. (2008); Lorens et al. (2004) with Walkowiak et al. (2011); Gordon et al. (2004a) with Gordon et al. (2004b). This reduced the total of number of unique studies to 32.

In addition, Appendix 2 (see Appendix 2 – Study overview in Supplemental Digital Content 2, http://links.lww.com/EANDH/A369) provides an overview of the judgment on eCAP-based fitting, study design and used CIs of each study. One study used Ineraid implants (Brown et al. 1996), while all other studies use modern CIs from Cochlear (22 studies), Advanced Bionics (7 studies), and MED-EL (2 studies). Further, most studies have compared eCAP threshold profiles with both T- and C-levels (23 studies), whereas a few studies made the comparison for either T-levels (1 study) or C-levels (8 studies). A total of 11 studies provided a group correlation coefficient for T-eCAP usable for meta-analysis (Fig. 2, studies without asterisk) and 12 studies for C-ECAP (Fig. 3, studies without asterisk). In addition, 3 studies provided individual correlations for both T-eCAP and C-eCAP (Franck & Norton 2001; Franck 2002; Potts et al. 2007; Holstad et al. 2009).

ROB Assessment

Table 2 shows the ROB scores from the assessment of all 32 studies on attrition bias, selection bias, outcome assessment bias, and analytical bias. A black dot indicates a positive score (bias present), a white dot a negative score (bias absent), and a question mark indicates that the paper did not provide enough information to score that bias. To summarize Table 2, only four studies had more than 10% attrition (Franck & Norton 2001; Franck 2002; Han et al. 2005; Akin et al. 2006, 2008; Holstad et al. 2009). However, note that most studies screened for available eCAPs before or during their research, because CI subjects without measurable eCAP are unusable. There was no clear evidence for studies suffering from selection bias, however, nine studies did not provide

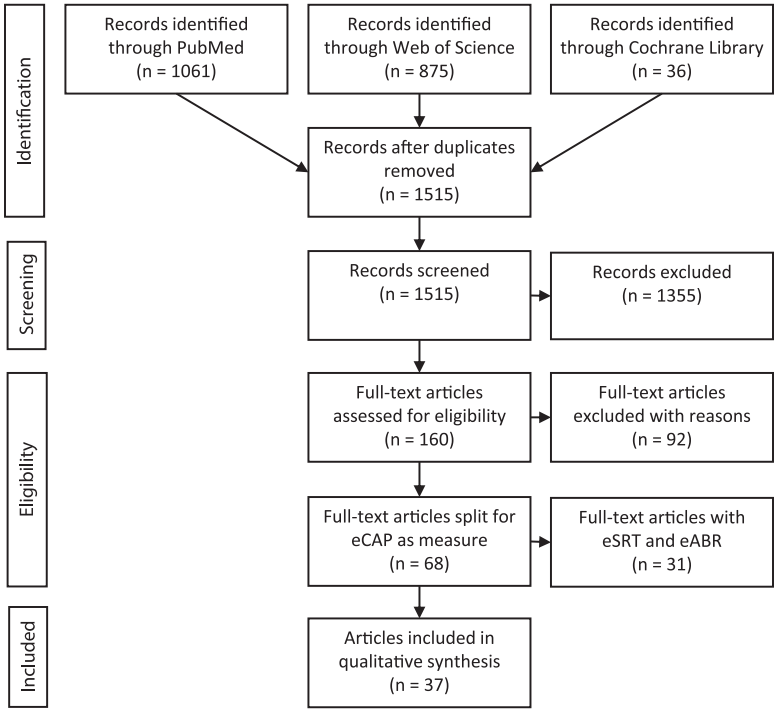

Fig. 1. PRISMA flow diagram. Adapted from *PLOS Med*, 6:e1000097. eCAP indicates evoked compound action potential; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

TABLE 2. Rating of the risk of bias analysis per study

	Study	Year	Attrition Bias	Selection Bias	Outcome Assessment Bias	Analytical Bias
	Potts et al	2007	○	○	○	○
	Franck and Norton/Franck	2001/2002	●	○	○	○
	Holstad et al.	2009	●	○	○	○
	Alvarez et al.	2010	○	○	○	●
	Cullington	2000	○	○	○	●
	Di Nardo	2003	○	○	○	●
	Hughes et al	2000	○	○	○	●
	Kaplan-Neeman et al	2004	○	○	○	●
	King	2006	○	○	○	●
	Mittal and Panwar	2009	○	○	○	●
	Morita et al.	2003	○	○	○	●
	Polak	2006	○	○	○	●
	Thai-Van et al.	2001/2004	○	○	○	●
	Van den Abbeele	2012	○	○	○	●
	Lorens et al./Walkowiak et al.	2004/2011	○	○	○	●
	Brown	1996	○	?	○	●
	Gordon	2004a/2004b	○	○	?	●
	Kiss	2003	○	○	?	●
	Lai	2009	○	○	?	●
	Muhaimeed	2010	○	○	?[c]	●
	Wesarg*	2010	○	?	○	●
	Pedley	2007	○	?	○	●
	Wolfe	2008	○	○	?[s]	●
	Cafarelli Dees	2005	○	○	●	●
	Smoorenburg	2002	○	○	●	●
	Caner	2007	○	?	?[s]	●
	Jeon	2010	○	?	?[s]	●
	Brown et al.	2000	○	?	●	●
	Botros and Psarros	2010	○	?	●	●
	Raghunandhan et al.	2014	○	?	?[s]	●
	Han et al.	2005	●	○	?[s]	●
	Akin et al.	2006/2008	●	?	?[s]	●
Total	32	37	4	9?	4/10?	29

A filled circle indicates a positive score, that is, the bias is present, while an open circle indicates the study did not suffer for that type of bias. When there was uncertainty about the risk of bias in a study by lack of data in the methods section, this was scored with a question mark.
*?At risk, not enough information available; ●positive score (bias present); ○negative score (bias absent); [s]use of Soundwave software (Advanced Bionics); [c]use of Custom Sound software (Cochlear); *use of three populations.*

sufficient information about the selection procedure or the randomization (Brown et al. 1996, 2000; Akin et al. 2006; Caner et al. 2007; Pedley et al. 2007; Botros & Psarros 2010; Jeon et al. 2010; Wesarg et al. 2010; Raghunandhan et al. 2014). These studies have an increased risk for selection bias and were scored with a question mark. Concerning outcome selection bias, three provided an inadequate description of the measuring procedure (Kiss et al. 2003; Gordon et al. 2004a, b; Lai et al. 2009). Seven studies used fitting software with embedded eCAP measurement feature, (Soundwave by Advanced Bionics or Custom Sound by Cochlear), while the use of this feature has not been reported explicitly. These studies have an increased risk of outcome selection bias and are also marked with a question mark (Han et al. 2005; Akin et al. 2006, 2008; Caner et al. 2007; Wolfe & Kasulis 2008; Jeon et al. 2010; Muhaimeed et al. 2010; Raghunandhan et al. 2014). Four studies suffered from inadequate blinding; they adjusted eCAP threshold profiles to match T- and C-levels (Brown et al. 2000; Smoorenburg et al. 2002; Cafarelli Dees et al. 2005; Botros & Psarros 2010). Wesarg et al. (2010) used 3 groups of subjects, with the third group making use of subjective fitting based on eCAP thresholds. Only three studies were not suffering from the analytical bias, providing individual T-eCAP and C-eCAP correlation coefficients (Franck & Norton 2001; Franck 2002; Potts et al. 2007; Holstad et al. 2009). In addition to Table 2, a more comprehensive overview for study analysis and assessment of different subject populations can be found in Appendices 3 (see Appendix 3 – Study analysis in Supplemental Digital Content 3, http://links.lww.com/EANDH/A370) and 4 (see Appendix 4 – Study populations in Supplemental Digital Content 4, http://links.lww.com/EANDH/A371), respectively.

Meta-Analysis

Meta-analyses for T-eCAP and C-eCAP are shown in Figures 2 and 3, respectively. The figures show study name, population size (subjects), correlation coefficient (r), and 95% c.i. for each study. Additionally, the study's weight in the meta-analysis is shown in the last two columns, separately for the fixed and random effects model. Results based on both fixed and random effects model are shown. Because the studies are heterogeneous, results based on the random effects model are more appropriate. A total of 390 subjects from 14 studies were analyzed for T-eCAP (Fig. 2). Pearson's correlation coefficients varied from $r = 0.24$ (Holstad et al. 2009) to $r = 0.89$ (Brown et al. 2000). The weighted pooled correlation for T-eCAP was weak ($r = 0.56$, CI 0.48 to 0.63).

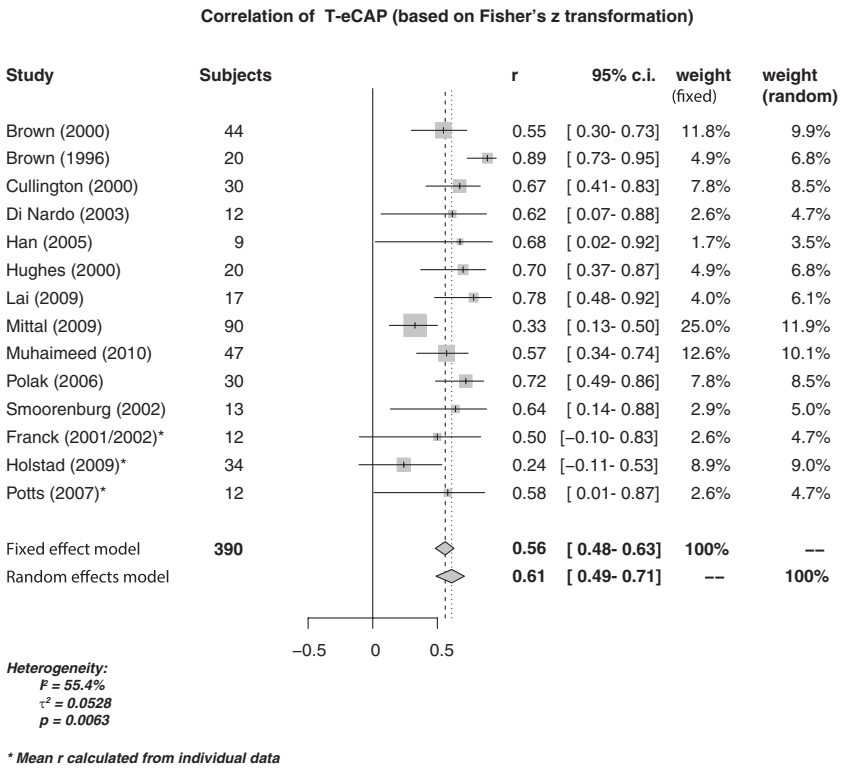

Fig. 2. Forest plot showing the meta-analysis of T-eCAP. The first and second column shows the included studies and number of subjects, respectively. In the middle, a graphical representation of the study results is depicted, whereby the gray square indicates the group size, the vertical line Pearson's *r*, and the horizontal line the 95% confidence interval of *r*. The values of *r*, 95% confidence interval, weight in the fixed model, and weight in the random model can be found in the last columns, respectively. The dark dotted line is the pooled correlation found for the fixed model, and the lighter dotted line is the pooled correlation found for the random model. T-eCAP indicates threshold evoked compound action potential.

The pooled correlation in the random effects model was similar ($r = 0.61$, 95% c.i. 0.49 to 0.71). The percentage of variance in study results attributable to heterogeneity (I^2) was 55.4%. For the C-eCAP (Fig. 3), a total of 444 subjects from 15 studies were analyzed. The correlation coefficients varied between $r = 0.26$ (Holstad et al. 2009) and $r = 0.80$ (Lai et al. 2009). The pooled correlations in the fixed and random effects models were identical ($r = 0.58$), though the c.i. was slightly broader for the random effects model. The I^2 for C-eCAP was 32.7%. Note that the correlation for Franck et al. (2002), Holstad et al. (2009), and Potts et al. (2007) was calculated based on individual correlations.

Figure 4 shows the results of the sensitivity analysis for the meta-analysis of both T-eCAP and C-eCAP. From left to right the outcomes of the meta-analyses are shown based on all studies, studies reporting group correlations, studies reporting individual correlations, studies with adequate blinding, studies with adults only, and studies with children only. The correlation coefficient was slightly lower for the "individual correlations" group (T-eCAP: $r = 0.36$ and C-eCAP: $r = 0.38$) and the "Children" group (T-eCAP: $r = 0.42$ and C-eCAP: $r = 0.35$). Notably, the T-eCAP correlation in children had an uninformatively large 95% c.i. due to the small sample size. The pooled average of groups with an adequate number of studies ("group correlations," "blinded," and "adults") showed no significant difference when comparing T-eCAP and C-eCAP (whiskers representing the 95% c.i. do overlap).

Individual Correlation Data

To investigate the use of eCAP for fitting individual subjects, comparison of eCAP and behavioral thresholds within individuals is highly preferable. However, only three studies reported individual T-eCAP and C-eCAP correlations (Franck & Norton 2001; Franck 2002; Potts et al. 2007; Holstad et al. 2009). In Figure 5, a histogram is plotted which shows the distribution of the individual correlation coefficients, separately for T-eCAP (top) and C-eCAP (bottom). The correlation coefficients were spread across a wide range. Franck et al. (2002) reported both the T-eCAP and C-eCAP data for 12 subjects, ranging from $r = -0.36$ to $r = 0.97$ for T-eCAP and from $r = -0.29$ to $r = 0.86$ for C-eCAP. The T-eCAP and C-eCAP data from Potts et al. (2007) (n = 15) revealed individual T-eCAP correlations ranging from $r = 0.07$ to $r = 0.88$ and C-eCAP correlations ranged from $r = 0.23$ to $r = 0.95$. Holstad et al. (2009) reported the largest group of individual correlation data (n = 36 subjects) for both T-eCAP and C-eCAP. For T-eCAP, correlations varied from $r = -0.67$ to $r = 0.97$, while for C-eCAP, the correlations varied from $r = -0.63$ to $r = 0.97$.

DISCUSSION

This systematic review evaluated 37 papers describing 32 unique studies for their evidence of eCAP-based fitting of CIs. The studies were reviewed using the PRISMA method and a ROB assessment. The ROB assessment was chosen because the overall study quality did not enable the common screening for level of evidence. The ROB assessment scored overall study quality on attrition bias, selection bias, outcome assessment bias, and analytical bias.

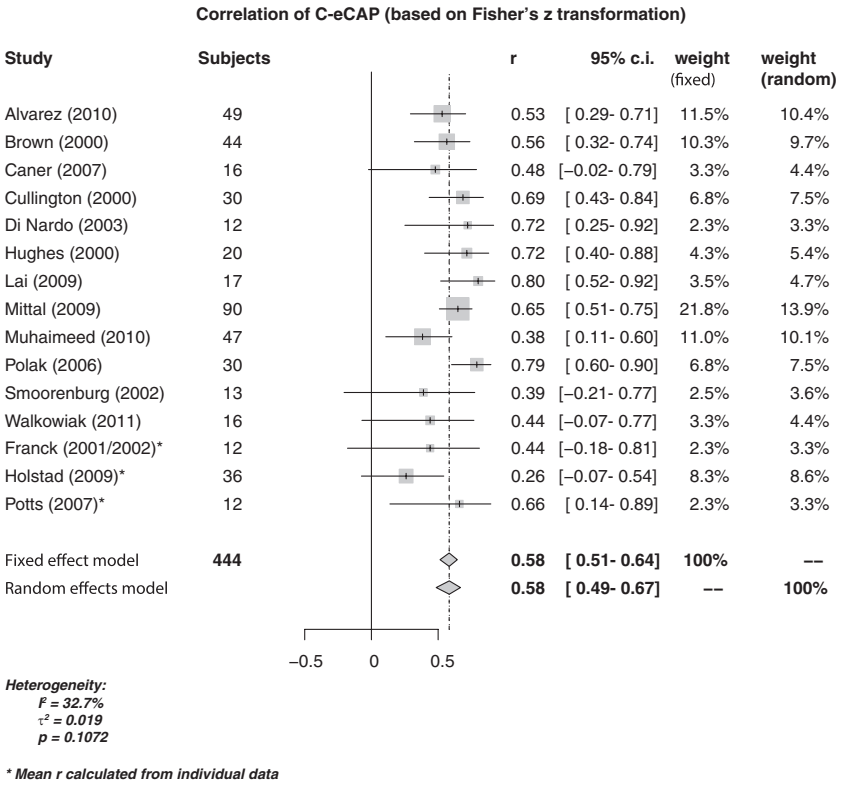

Fig. 3. Forest plot showing the meta-analysis of C-eCAP. The results were presented similarly as in Figure 2. eCAP indicates evoked compound action potential.

ROB Assessment

Attrition Bias • Attrition more than 10% was found in only four studies (Franck & Norton 2001; Franck 2002; Han et al. 2005; Akin et al. 2006, 2008; Holstad et al. 2009). However, there was no clear consensus on reporting CI users with poor eCAPs; some studies exclude poor responders before the study, whereas others count these subjects as lost in follow-up. Since the exclusion of subjects with poor or no measurable eCAPs will not necessarily influence the results, it would be valid to exclude these poor eCAP responders. Therefore, we did not count poor responders as attrition in the ROB assessment. On the other hand, it is important to report the amount of poor eCAP responders, because it provides insight in the success rate and applicability of objective fitting for CI recipients. The exclusion of poor eCAP responders can therefore also be seen as a selection bias.

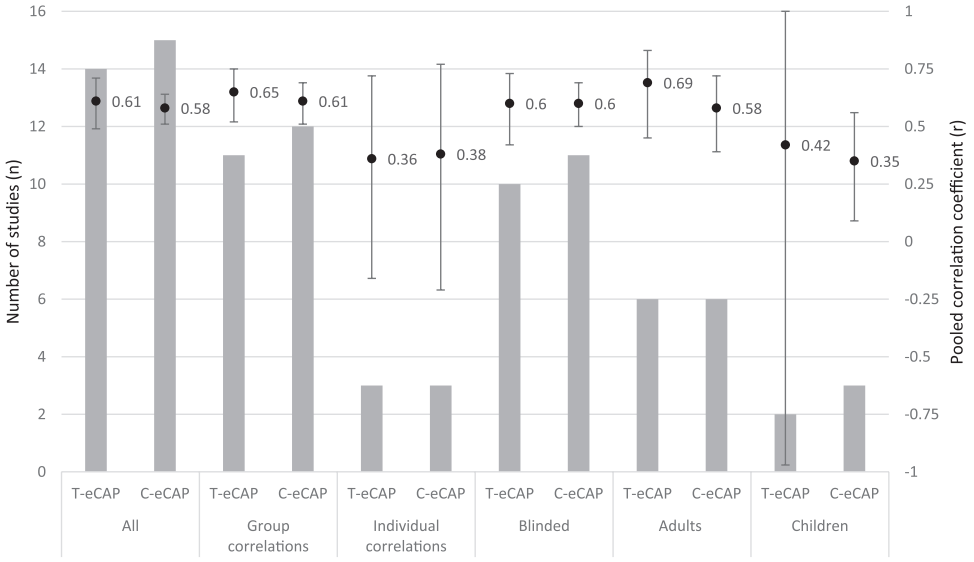

Fig. 4. Sensitivity analysis graph showing in gray bars the number of studies included (left ordinate) and in black dots the pooled correlation coefficient (right ordinate) for each analyzed group. The whiskers indicate the 95% confidence intervals of the pooled correlation coefficient. From left to right, the outcomes of the meta-analyses are shown for: all studies, studies based on group correlations, studies based on individual correlations, studies with adequate blinding, studies with adults only, and studies with children only. eCAP indicates evoked compound action potential.

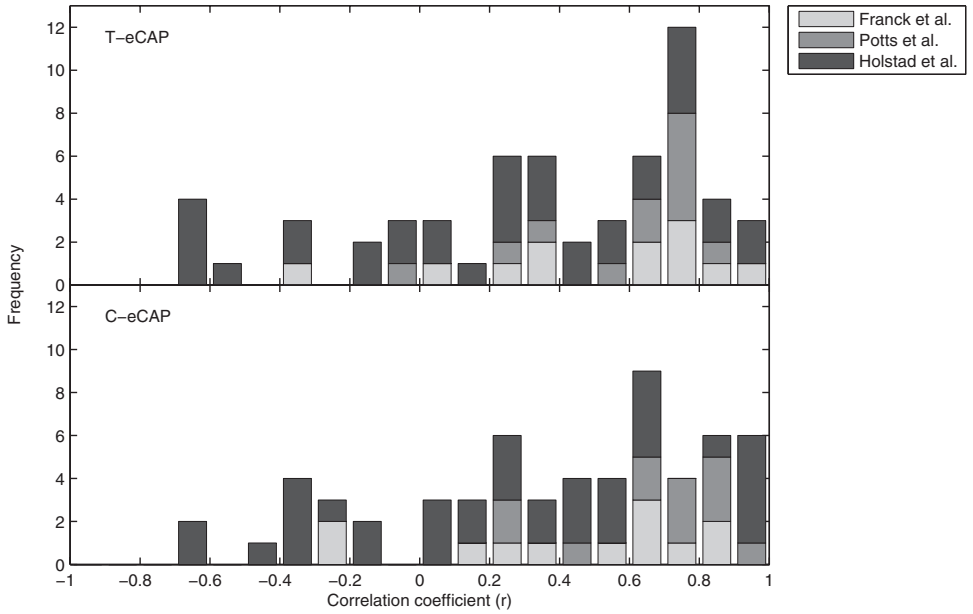

Fig. 5. Histogram of T-eCAP (top) and C-eCAP (bottom) correlation coefficients (*x* axis) from individual subjects as reported by Franck et al. (2001/2002), Potts et al. (2007), and Holstad et al. (2009). Correlation coefficients were grouped in bins with a width of 0.1. Black indicates individuals from the study of Holstad et al., dark gray from the study of Potts et al., and light gray from the study of Franck et al. eCAP indicates evoked compound action potential.

Selection bias • We found that the studied populations differed considerably between studies. Some studies used a heterogenic group of CI recipients, whereas other studies used specific subpopulations, for example, prelinguals, postlinguals, children or adults (see Appendix 3 – Study analysis in Supplemental Digital Content 3, http://links.lww.com/EANDH/A370). Therefore, the selection bias was scored with respect to the intended population. As long as the subjects were selected randomly from within the intended subpopulation and there was a proper representation of the population intended for the conclusion, we scored studies positive for randomization. When the randomization was not described clearly, the study was scored by a question mark indicating that there is an increased risk on selection bias (Table 2).

A more hidden form of selection bias is the overrepresentation of one manufacturer (Cochlear) both in literature and the reviewed studies: 24 Cochlear, 7 Advanced bionics, 1 Ineraid, and 2 MED-EL (see Appendix 2 – Study overview in Supplemental Digital Content 2, http://links.lww.com/EANDH/A369). Brand-related differences in hardware (e.g., noise floor) and software (e.g., eCAP detection method, linear vs logarithmic current scale) might lead to differences in eCAP thresholds and fitting levels. Consequently, the correlation between these two measures could be (slightly) different for each manufacturer. Therefore, a more balanced representation of all manufacturers is desirable to get a more general answer on the question whether eCAP could be used for objective fitting.

Outcome Assessment Bias • The use of objective measures to set the behavioral fitting parameters was scored as a lack of blinding. Such data cannot be used to investigate the predictive value of eCAP thresholds for fitting levels, because the behavioral data are not independent from objective measurements. The risk for this specific form of bias is especially high in more recent studies, as modern fitting software (Soundwave, ART, and AutoNRT) enables the user to easily adjust the behavioral map by using the objectively measured eCAP data. Unfortunately, it was not feasible to determine the exact influence of this fitting software. To avoid underreporting outcome assessment bias, we scored studies that used modern fitting software while the use of the eCAP feature has not been reported explicitly as "unknown" for blinding.

Of special interest was the use of behavioral data to adjust the objective threshold profile. Brown et al. (2000) introduced a method to shift the eCAP threshold profile toward hearing level using the behavioral threshold at one electrode contact. The shift does not influence the correlation between the objective and behavioral thresholds as long as it is performed within subjects. For this reason, applying the shift in combination with a within-subject correlation, for example as Franck and Norton (2001), was not scored as outcome assessment bias. For group correlation, the shift could increase the correlation dramatically (Franck & Norton 2001). However, group correlation does not provide reliable results for individual patients (see section "Analytical Bias'). Therefore, shifting eCAP threshold before a group correlation received a positive score for outcome assessment bias, for example as Brown et al. In addition to the shift, Smoorenburg et al. (2002) introduced a tilt to further improve the fit between the objective and behavioral profiles, better known as the "shift and tilt" method. However, the "shift and tilt" approach provides eCAP threshold profiles which are no longer fully independent from the behavioral profiles. Therefore, the use of the "shift and tilt" approach was scored as an outcome assessment bias, for example, as in Smoorenburg et al. and Cafarelli Dees et al. (2005). In the study of Botros & Psarros (2010), shifted eCAP threshold profiles were additionally scaled. This scaling resulted in flatter profiles at higher stimulation level, because the scaling factor was inversely related to the stimulus level. Though less obvious, the eCAP-based profiles were not independent of the behavioral profiles, thus, these studies were scored positive for outcome assessment bias.

Analytical Bias • Besides properly collected data, a correct (statistical) analysis is also a prerequisite for reliable results and valid conclusions. Therefore, all studies were scored on analytical bias. Van der Beek et al. (2015) showed a great intersubject

variability in both eCAP thresholds and behavioral T/C-levels. The correlation analysis between eCAP thresholds and behavioral fitting levels should therefore ideally be based on subject level. However, only three studies showed the correlation within individual subjects (Franck & Norton 2001; Franck 2002; Potts et al. 2007; Holstad et al. 2009). The correlation coefficients reported in these studies (plotted in a histogram in Fig. 5) show great variation per individual subjects. Based on their results, Holstad et al. (2009) suggested that the individual variation was too large for reliable objective fitting of children without the use of subjective data. Potts et al. (2007) mentioned that when behavioral measures cannot be obtained consistently, eCAP thresholds can provide valuable information about the level associated with an auditory response on each electrode. However, eCAP thresholds should be used conservatively to create an initial speech processor map. In contrast to these three studies, all other studies did not take into account the within-subject correlation; they based their conclusion on a grouped correlation only. The problem of a group correlation is that the correlation is driven by the (large) intersubject variation and can be qualitatively different form the within-subject association. Being not aware of this effect, which is also called the Simpsons' Paradox (Julious & Mullee 1994), will result in a high risk for incorrect conclusions. Given the contradictory outcomes and conclusions of several studies (see Appendix 2 – Study overview in Supplemental Digital Content 2, http://links.lww.com/EANDH/A369), the suspicion arises that not all studies are calculating the correlations in a proper way. This notion is supported by the fact that studies using grouped correlations were positive about the role of eCAP data in fitting procedures (Morita et al. 2003; Kaplan-Neeman et al. 2004; Pedley et al. 2007; Lai et al. 2009; Mittal & Panwar 2009; Botros & Psarros 2010; Muhaimeed et al. 2010; Walkowiak et al. 2011), while Holstad et al. (2009) and Potts et al. (2007), who base their analysis on individual correlations, are dismissive.

Meta-Analysis

A meta-analysis on the included studies that reported a Pearson's correlation coefficient revealed that the use of eCAP thresholds is a weak predictor of both T- and C-levels. We found a pooled correlation of $r = 0.61$ for T-eCAP and C-eCAP had a slightly lower pooled correlation of $r = 0.58$. Note that two types of correlation coefficients are included in the analysis: grouped correlations and means of individual correlations (studies with asterisk). Whereas the majority of the reviewed studies reported a group correlation, the individual correlations were included as well, because they provide useful information (see section "Analytical Bias"). The sensitivity analysis showed that including both types of correlation coefficients did not change the results of the meta-analysis significantly (Fig. 4). Franck & Norton (2001) provided both grouped and individual correlations. Comparing both types of correlation coefficients revealed that the group correlation between eCAP thresholds (visual) and T-levels (80 Hz) was stronger than the mean individual correlation ($r = 0.77$ vs $r = 0.50$, respectively). However, similar comparison for C-eCAP revealed the opposite: a group correlation of $r = 0.03$ and a mean individual correlation of $r = 0.44$. This example clearly demonstrates that (1) individual correlations can be totally different than a grouped correlation on the same data (Simpson's paradox), and (2) the choice of analysis method has major consequences for the results and conclusion.

The majority of the studies included in the T-eCAP and C-eCAP meta-analysis used Cochlear devices. From the 15 studies, only 2 studies used implants of AB (Han et al. 2005; Caner et al. 2007) and 2 studies of MED-EL (Alvarez et al. 2010; Walkowiak et al. 2011). Due to the low number of Advanced Bionics and MED-EL studies, we could not statistically test the effect of manufacturer on the pooled correlation coefficients. However, based on the distribution of the correlation coefficients of the Cochlear studies, we might conclude that the results of the meta-analysis are representative for Cochlear. Further, the sensitivity analysis did not show any significant difference when a meta-analysis performed on all studies was compared with the meta-analysis performed by selectively incorporating studies with adequate blinding, studies with children only, and studies with adults only (Fig. 4). This indicates that the meta-analysis was robust for all subpopulations.

Toward eCAP-Based Fitting

This review revealed several issues with respect to study design and statistical analysis, as well as contradictory outcomes between different studies (see Appendix 2 – Study overview in Supplemental Digital Content 2, http://links.lww.com/EANDH/A369) and a large variation in individual correlations (Fig. 5). Hence, we must conclude that there is currently no evidence for the validity of eCAP-based fitting of CIs. To be able to answer the question whether eCAP thresholds can predict fitting levels, at least the biases reported in this study must be avoided. In other words, the subjects must be selected randomly and the exclusion of poor eCAP responders should be reported, because this affects the success rate of eCAP-based fitting. Further, the behavioral levels must be measured blinded from the eCAP measurements, and both the eCAP and behavioral measurements should be described in detail. Finally, the correlation between eCAP and behavioral levels must be investigated within individual subjects to draw valid conclusions for eCAP-based fitting of individuals.

In addition, we want to highlight the following considerations in eCAP threshold research:

Measurement Data • Review of the applied fitting strategies showed that most of the studies did not elaborate in detail on the applied strategy. This challenges the systematic review of eCAP-based fitting, because it is unknown whether the different study results are based on comparable data. Three studies reported that the T-levels were set as 10% of the C-level (default in the SoundWave fitting software of Advanced Bionics), but these levels were not used in a correlation analysis (Caner et al. 2007; Akin et al. 2008; Raghunandhan et al. 2014). One study reported that the C-level was typically set a predefined number of programming units above T-level, because they are dealing with children (Hughes et al. 2000). All other studies reported that the behavioral levels were measured, fitted by an audiologist, or they only mentioned that the fitting levels were collected. When reviewing the fitting strategies, we found many differences due to manufacturer, used software, measurement properties, audiologist experience, and CI-center. A few studies used comparable fitting strategies, for example, the default fitting method recommended by the manufacturer, or a fitting method based on the Hughson-Westlake approach (Thai-Van et al. 2004; Pedley et al. 2007; Jeon et al. 2010).

It is likely that the encountered methodological differences affect the actual fitting levels and thus the correlation. However, it was not possible to include the applied methods in the ROB- and meta-analysis; they could not be classified and the number of available studies was too low for statistical analysis.

Additionally, one might wonder whether current CI devices and fitting software do a better job than previous versions thereby improving the correlation. However, the Figures 2 and 3 do not support this; more recent studies did not show a better correlation between eCAP and behavioral measures. For example, Figure 2 shows that the highest correlation coefficients originate from the oldest study (Brown et al. 1996).

Stimulation Rate • Another factor possibly affecting the correlation is the applied stimulation rate. Behavioral fitting levels are routinely measured at high-rate pulse trains (250 to 3500 Hz) (Arora et al. 2012), while eCAP-based telemetry is performed at much lower rates (35 to 80 Hz). Brown et al. (1998) and Franck et al. (2001) found that the correlation between behavioral and eCAP thresholds is best at equal stimulation rate for behavioral and eCAP stimulation. Based on these findings, we can conclude that, if the eCAP would be used to predict fitting levels, the pulse rate for eCAP measurements ideally should be close to the (high) rate used for behavioral measurements. However, Charasse et al. (2004) showed that increasing the stimulus frequency for the measurement of eCAP responses saves time during measurements but has a degrading effect on the quality and amplitude of the eCAP response. Further, McKay et al. (2013) investigated whether high-rate behavioral thresholds can be predicted by eCAP thresholds combined with rate-dependent eCAP characteristics (e.g., loudness growth and temporal integration). However, they still conclude that it is unlikely that the lower rate eCAP thresholds can be combined with the high-rate behavioral fitting levels.

Measurement Error • When comparing measurements, the measurement error should be considered to correctly interpret the differences. However, we encountered no study that included a measurement error for the eCAP and behavioral measurements. ECAP thresholds and fitting levels were handled as fixed data points, even though they have an uncertainty depending on the measurement properties and conditions. Therefore, the precision of the measurements probably differs between studies and affects the presented correlations. Potentially, including the measurement error will lead to better measurements and could enhance the usability of eCAPs in clinical practice.

Speech Perception • Several papers were encountered that used speech perception as outcome measure for eCAP-based fitting rather than the behavioral fitting levels (Frijns et al. 2002; Sun et al. 2004; Guedes et al. 2007; Cosetti et al. 2010; D'Elia et al. 2012; Bournique et al. 2013; Zhang et al. 2013; Scheperle & Abbas 2015). Seyle and Brown (2002) even used different types of eCAP-based fitting maps to investigate objective fitting with speech perception as outcome measure. These studies propose that speech perception, though it is subjective, is more directly related to the quality of hearing in CI recipients than the fitting levels. Consequently, speech performance potentially is a better outcome measure for assessing eCAP-based fitting than behavioral T/C-levels (Seyle & Brown 2002; Guedes et al. 2007; Zhang et al. 2013). Although it is an interesting topic, it is beyond the scope of this article to review the objective fitting based on speech perception, for example, whether and, if so, which speech perception test is best suited for this purpose.

CONCLUSIONS

This systematic review shows that many of the included studies dealt with methodological shortcomings in randomization, blinding, population etiology, and statistical analysis. Considering statistical analysis, studies building their conclusions on group analysis, thereby negating within-subject variation, have a high risk on analytical bias whereby the conclusion is not representative for individual subjects. We conclude that most of the reviewed studies are not optimal to answer the research question whether the eCAP could be used to predict fitting levels of individual CI recipients. Additionally, the three studies which applied appropriate statistical analyses do not support the use of eCAP threshold data only for CI fitting purposes. In future studies, we recommend emphasizing correct blinding, a well-defined study design and the use of appropriate statistical analyses. Finally, we point to multiple studies which suggest speech perception as potentially better outcome measure for assessing eCAP-based fitting, rather than comparing objective eCAP thresholds to behavioral fitting levels.

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