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Pattern Electroretinogram in Ocular Hypertension, Glaucoma Suspect and Early Manifest Glaucoma Eyes

A Systematic Review and Meta-analysis

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Topic: To provide standardized confidence limits of the transient pattern electroretinogram (tPERG) P50 and N95 and steady state pattern electroretinogram (ssPERG) amplitudes in normal controls as compared to ocular hypertension (OHT), glaucoma suspect (GS), or early manifest glaucoma (EMG) eyes.

Clinical Relevance: The identification of standardized confidence limits in the context of pattern electroretinogram (PERG) might overcome the high intrinsic variability of the measure, and it might lead to a more intuitive understanding of the results as well as to an easier comparison of data from multiple tests, sites, and operators.

Methods: The study protocol was prospectively registered on the International Prospective Register of Systematic Reviews (ID: CRD42022370032). A literature search was conducted on PubMed, Web of Science, and Scopus. Studies comparing PERG raw data in normal control eyes as compared to OHT, GS, or EMG were included. The risk of bias was assessed using the National Institute for Health and Clinical Excellence quality assessment tool. The main outcome was the P50, N95, and ssPERG amplitude difference between the control and the study groups' eyes. The standardized mean difference was calculated as a measure of the effect size for the primary outcome. A subanalysis was conducted based on the type of electrodes adopted for the PERG measurements (invasive vs. noninvasive).

Results: Of the 4580 eligible papers, only 23 were included (1754 eyes). Statistically significant amplitude differences were found in the P50, N95, and ssPERG amplitudes between normal controls and OHT, GS, and EMG eyes. The highest standardized mean difference values were observed in the ssPERG amplitude in all 3 sets of comparison. The subanalysis did not reveal any statistically significant differences between invasive and noninvasive recording strategies.

Conclusions: The use of standardized values as the main outcome measures in the context of the PERG data analysis is a valid approach, normalizing several confounding factors which have affected the clinical utility of PERG both for individual patients and in clinical trials. Steady state PERG apparently better discriminates diseased eyes compared to tPERG. The adoption of skin-active electrodes is able to adequately discriminate between healthy and diseased statuses.

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According to the International Society for Clinical Electrophysiology of Vision, pattern electroretinogram (PERG) is defined as a "retinal biopotential evoked by a temporally modulated patterned stimulus of constant mean luminance."[1]

A growing body of evidence suggests PERG is a reliable proxy for the viability of retinal ganglion cells (RGCs) and is an objective and reliable index of RGC loss.[2,3] For instance, PERG has been shown to be altered in eyes with ocular hypertension (OHT) and early manifest glaucoma (EMG).[4,5] Nonetheless, the reduction of intraocular pressure (IOP) has been reported to improve PERG, thus supporting the idea of a strict relationship between IOP, RGC functionality, and PERG.[6]

Despite its potential as a diagnostic tool for the early detection of glaucoma, several issues still prevent the widespread adoption of PERG in ophthalmic clinical practice. Among them, the high interobserver variability is largely

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responsible for the lack of standard international reference ranges for PERG measurements.[1] While the adoption of absolute values as PERG references might be difficult due to the intrinsic variability of the methodology, the adoption of standardized measures might help clinicians both in the diagnosis and follow-up of disease statuses (e.g., OHT, glaucoma suspect [GS], and EMG).

Based on the temporal frequency of the stimulus, 2 different PERG waveforms can be elicited, defined as transient or standard pattern electroretinogram (tPERG) and steady state pattern electroretinogram (ssPERG).[1,7] The tPERG waveform incorporates 2 main components, the P50 (a positive peak at approximately 50 ms) and the N95 (a negative trough of more variable peak time at around 95 ms in healthy subjects). The ssPERG waveform is derived from a discrete Fourier analysis which allows isolation of the second harmonic featured by a specific amplitude and phase.

Both tPERG and ssPERG recordings can be performed either invasively or noninvasively.[1] In fact, the electrode can be placed either on the corneal surface or on the bulbar conjunctiva adjacent to the inferior limbus of the cornea for invasive recordings, while noninvasive recordings involve placing the electrode on the skin of the lower lid.[8] Several types of invasive electrodes are available, including the Hawlina−Konec loop[9], gold foil[10], and Dawson−Trick−Litzkow[11] electrodes. Currently, the International Society for Clinical Electrophysiology of Vision does not recommend using skin electrodes for recording the PERG, as they result in lower amplitudes compared to using electrodes in contact with the eye.[1] However, it has been reported that skin electrodes are more stable than corneal electrodes, resulting in a less variable signal.[3,5,8] This is particularly important as invasive methods can be uncomfortable for the patient and may carry a higher risk of complications. Moreover, using skin electrodes can often be a more practical and cost-effective approach, as it does not require the use of specialized equipment or the expertise of a trained technician.

The main aim of this systematic review and meta-analysis is to provide standardized confidence limits of the P50, N95, and ssPERG amplitudes for a population of normal eyes as compared with eyes classified as OHT, GS, or EMG. The identification and adoption of standardized limits in the context of PERG would help in overcoming the high intrinsic variability of the measure. This could eventually lead to a more intuitive understanding of the results as well as an easier comparison of data from multiple tests, sites, and operators. We will also report the pooled mean and 95% confidence intervals (CIs) per each main outcome measure (i.e., P50, N95, and ssPERG amplitudes) in all 4 conditions (i.e., normal, OHT, GS, and EMG) as well as according to the different recording strategies used (i.e., invasive vs. noninvasive).

Methods

This systematic review and meta-analysis conformed to the Cochrane Handbook, and results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] Since all the reported data were obtained from the available published literature, neither institutional review board approval nor informed consent were required for this study. The study protocol was prospectively registered on the International Prospective Register of Systematic Reviews (ID: CRD42022370032). No amendments to the original protocol have been made.

Inclusion and Exclusion Criteria

The Patient-Intervention-Comparator-Outcome-Study Type framework was used in developing the literature search strategy[13] as follows: patients (P), male and female adults worldwide (> 18 years); investigated condition (I), OHT, GS, and EMG; comparator (C), healthy control patients, defined as having a best-corrected visual acuity of 20/25 or better without any concomitant systemic or ocular conditions affecting visual function or a previous history of any intraocular surgery; outcome (O), included tPERG P50 and N95 amplitudes and ssPERG amplitude difference; and study type (S), retrospective case-control and prospective cross-sectional studies.

Concerning diseased status classifications, OHT was defined as the presence of a consistently raised IOP (i.e., > 21 mmHg) on ≥ 2 separate occasions, normal standard automated perimetry with a mean deviation of > −2 decibels (dB), pattern standard deviation with $P > 5\%$, and clinically normal optic disc on slit-lamp (i.e., vertical cup-to-disc [C/D] ratio < 0.6; C/D ratio asymmetry ≤ 0.2; no optic disc excavation; and no thinning of the neuroretinal rim, notching, or peripapillary splinter hemorrhages).[14−17] Glaucoma suspect was defined as the presence of ophthalmoscopic signs suggestive of glaucomatous damage, with or without IOP > 21 mmHg, without any visual field defect detectable by means of standard automated perimetry.[14,15] Early manifest glaucoma was defined as the presence of glaucomatous changes at the optic disc (i.e., vertical C/D > 0.6; C/D ratio asymmetry ≥ 0.2; optic disc excavation; and thinning of the neuroretinal rim, notching, or peripapillary splinter hemorrhages) and corresponding reproducible visual field loss (i.e., ≥ 3 adjacent nonedged points of > 5 dB loss or ≥ 2 points > 10 dB loss confirmed by repeated testing). Several classifications of EMG currently exist. Studies were included if the Hodapp−Parrish−Anderson, the American Academy of Ophthalmology, or the European Glaucoma Society defining criteria were used.[14,15,18]

Specifically, studies were included if they reported PERG raw data (i.e., the means of P50, N95, or ssPERG amplitude) in normal control eyes as compared to OHT, GS, or EMG. As a result, 3 different orders of comparison were imposed (i.e., normal vs. OHT; normal vs. GS; and normal vs. EMG). For each of these, 3 different sets of analysis were conducted for P50, N95, and ssPERG amplitude, respectively.

No limitations were imposed regarding the use of ocular hypotensive drugs or previous glaucoma surgery in any of the included groups (i.e., OHT, GS, and EMG). While IOP reduction has been demonstrated to improve RGC function as assessed by PERG, we believed including previously treated eyes would not affect the reliability of our results.[6] In fact, assuming a normal distribution of treated eyes among different groups (i.e., OHT, GS, and EMG), the impact of the hypotensive effect on the PERG data would be equally distributed and thus would not exert a major influence on pooled results.

Studies were excluded if enrolled patients were previously or currently treated with coenzyme Q10, nicergoline, or citicoline, all of which are known to improve the PERG response. Additional exclusion criteria included studies that (a) were not in English, (b) were in the form of either a conference abstract, a review, a case

report, a book chapter, or a letter to the editor, or (c) were not available in full text form.

Data Source and Study Searching

An electronic search was performed on PubMed, Web of Science, and Scopus using relevant keywords, phrases, and medical subject heading terms. The last literature search was performed on June 1, 2022. No time limits were imposed. The search strings applied for different databases are reported in Supplementary Material (S1). The reference list of each selected article was then checked to screen for additional relevant studies, as per the snowballing method.

Data Extraction

The reference lists from the 3 databases were merged, and the duplicates were removed using the reference management software Rayyan.[19] After title and abstract screening, the full text of remaining papers was analyzed. The process was independently conducted by 2 reviewers (G.G.A. and T.H.C.). Any discrepancies in the selection process were resolved by consensus or with the help of a third reviewer (F.A.). Data extraction was conducted by 2 reviewers (G.G.A. and T.H.C.). No automation tools were used in the process. Extracted data included author and year of publication; study design; location of the study; funding sources; total number of screened eyes in normal controls, OHT, GS, and EMG groups; number of female subjects in each group; age and its standard deviation (SD) per each group; IOP and its SD per each group; mean deviation and its SD per each group; inclusion and exclusion criteria; type of PERG recording modality (i.e., tPERG or ssPERG) adopted; type of PERG recording machine adopted; type of electrodes adopted; and amplitude and its SD of P50, N95, and ssPERG wave per each group.

Data extracted from selected papers were archived in a customized Excel spreadsheet with forced choice entry criteria. Dichotomous variables were reported by counts and percentages, while continuous variables were reported as mean ± SD. No missing data were identified.

Risk of Bias and Study Quality Assessment

Two reviewers independently evaluated the quality of the included studies according to the National Institute for Health and Clinical Excellence quality assessment tool.

Data Synthesis and Statistical Analysis

The analysis was performed using the *meta* package in R software for statistical computing (R version 1.4.1106). A fixed-effect model was applied in the presence of a number of studies ≤ 5 or whenever a low level of heterogeneity was found. Otherwise, a randomized mixed-effect model was preferred, as recommended by the Cochrane Handbook for Systematic Review of Interventions.[20]

The unit of analysis adopted for the evaluation of demographic data was the number of included patients. Otherwise, the unit of analysis corresponded to the number of eyes with a specified outcome.

Logit transformation of data was carried out for the analysis of overall proportions. The mean difference was calculated as a measure of effect size to compare continuous variables. Standardized mean difference (SMD) was calculated to compare P50, N95, and ssPERG amplitude data in the control group and in OHT, GS, and EMG eyes. In contrast to unstandardized mean differences, and as pointed out in the Cochrane Handbook, SMD expresses the difference between 2 groups in units of SD.[20,21] Notably, the SMD is calculated according to the following formula:

$$SMD = \frac{Difference\ in\ mean\ outcome\ between\ groups}{Standard\ deviation\ of\ outcome\ among\ participants}$$

The standardization has the effect that SMD = 1 always means that the 2 groups' mean values are 1 SD away from each other, and SMD = 2 then represents a difference of 2 SDs, and so forth.[20,21]

In line with the Cochrane Handbook, the SMD was estimated using *Hedges' g* and its 95% CI. In particular, *Hedges' g* is an important measure that corrects for biases due to small sample sizes. Details on *Hedges' g* formula can be obtained from the original publication by Larry V. Hedges.[22] As extensively reported in the literature, and citing Yang and Dalton's Statistical Analysis System (SAS) Global Forum 2012 paper, SMD can be treated as equivalent to a z-score of a standard normal distribution.[23–31] In fact, z-score is measured as:

$$z - \text{score} = \frac{x - \mu}{\sigma}$$

with x being the observed value, μ being the mean in the sample, and σ being its SD. As such, 1 SD equals 1 z-score.

A P value < 0.05 was considered statistically significant.

Based on the type of electrode adopted for the PERG measurements, studies were classified into 2 groups (i.e., invasive, noninvasive), and a subanalysis was conducted accordingly.

Cochran's Q was calculated as a measure of heterogeneity and checked by P value. We also reported I^2 statistic results, which quantify heterogeneity regardless of the number of included studies. The maximum-likelihood estimator was used to estimate the between-study variance (τ^2). The influence analysis was performed using the "Influence Analysis" function in R, and a Baujat plot was consequently created. The "find.outliers" function was used to detect any outliers presenting their 95% CI lying outside the 95% CI of the pooled effect.

Results

Electronic Database Search Results and General Features of the Studies Included

A total of 4580 eligible papers (404 from PubMed, 366 from Web of Science, and 3810 from Scopus) were retrieved from the preliminary search on electronic databases. After the automatic removal of duplicates and the screening of both titles and abstracts, the full text of 108 manuscripts was assessed for eligibility. Twenty-three articles published between 1988 and 2021 were included for the qualitative and the quantitative synthesis (Fig 1).[32–54] The reasons for the exclusion of 85 articles are summarized in Figure 1. Among the 23 included works, 2 retrospective case-control studies[32,38] and 21 cross-sectional studies were identified.[33–37,39–54] A total of 1754 eyes were identified, of which 742 were healthy controls, 429 OHT, 248 GS, and 335 EMG. Demographic and clinical features of the pooled cohort are summarized in Table 1. Among the 23 eligible studies, 14 were conducted in Europe[36,37,39,40,42–45,47–52], 4 in Asia[32,33,38,41], 3 in North America[46,53,54], and 2 in Africa.[34,35] Inclusion and exclusion criteria for each study are summarized in Supplementary Material S2.

From the qualitative analysis of the included studies, a large variability in PERG recording protocols emerged

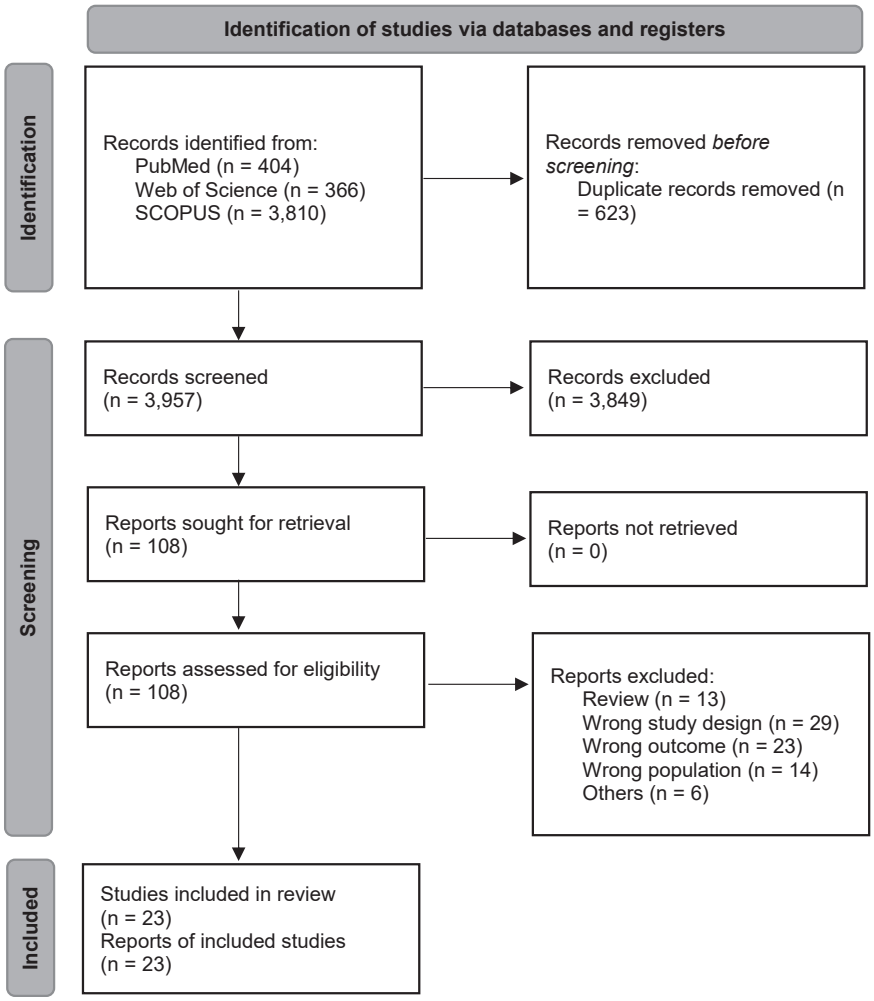

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses Flowchart. Reasons for exclusion are reported step-by-step on the right.

(Supplementary Material S3). Specifically, tPERG was measured in 16 out of the 23 (70%) included articles[32–38,40–43,45,48,49,51,53], while ssPERG was evaluated in the remaining 7 (30%).[39,44,46,47,50,52,54] Additional differences were found in the type, shape, material, and site of placement of the electrodes (S3). Specifically, the PERG recording was conducted noninvasively in 14 of the 23 studies (61%).[32,33,35,37–40,42–44,46–48,50] While reference electrode position was not reported in 1 study (9%),[43] the active electrode was placed on the skin of the lower eyelid in 10 cases (77%)[32,33,39,40,42,44,46–48,50] and on the skin of the ipsilateral temple and medial canthus in the remaining 3 (23%) (S3).[35,37,38] In the context of invasive PERG recording strategies, Hawlina–Konec loop, gold foil, and Dawson–Trick–Litzkow electrodes were used in 2

Table 1. Demographic and Clinical Features of the Selected Cohort

	Normal	OHT	GS	EMG
Number of eyes	742	429	248	335
Female [% (95% CI)]	49.3 (43.6–55.1)	50.8 (42.1–59.4)	54.9 (47.8–61.7)	52.5 (43.5–61.4)
Age [mean (95% CI)]	51.3 (47.9–54.5)	51.7 (47.7–55.6)	51.6 (42.3–60.9)	53.8 (49.2–58.4)
IOP [mean (95% CI)]	15.7 (13.9–17.6)	22.9 (20.5–25.5)	17.8 (15.9–19.6)	19.9 (15.1–24.8)
MD [mean (95% CI)]	−0.63 (−1.42 to 0.17)	−0.87 (−2.25 to 0.49)	−0.79 (−1.78 to 0.19)	−2.68 (−3.11 to −2.26)

CI = confidence interval; EMG = early manifest glaucoma; GS = glaucoma suspect; IOP = intraocular pressure; MD = mean deviation; OHT = ocular hypertension.

(22%),[34,36] 1 (11%),[54] and 6 (67%)[35,41,45,49,52,53] cases, respectively (S3). Reference electrode position was not reported in 1 study (9%) (S3).[43]

In 12 of 16 (75%) tPERG studies, the P50 amplitude was calculated from the trough of N35 to the peak of P50, and the N95 amplitude was measured from the peak of P50 to the trough of N95.[32,34,35,37,38,40,42,45,48,49,51,53] No information regarding the calculation method for the PERG amplitude was provided by the remaining 4 studies (25%).[33,36,41,43] Regarding ssPERG, the amplitude of the second harmonic was analyzed with the Fourier transform in 4 out of 7 studies (57%).[39,47,50,54]

Methodological Quality of Included Studies

Table 2 summarizes the risk of bias of included studies using the National Institute for Health and Clinical Excellence quality assessment tool. The risk of bias assessment showed a generally moderate quality of included studies, with a median score of 5.0. Notably, none of the included studies were multicentric, and none of them reported a consecutive patient enrollment, thus enhancing the risk of selection bias. In addition, 9 of the 23 studies (39%) did not clearly report inclusion criteria. Finally, 7 of the studies (30%) received external funding, an element which has been reported to influence data analysis, interpretation of findings, and the likelihood that favorable results are reported.[55]

PERG Data Differences Between Normal and OHT Eyes

Overall, 13 studies variably report information regarding PERG in normal versus OHT eyes, of which 9 (57%)[35,37,40,42,45,48,49,51,53] and 4 (43%)[44,47,50,54] were in the context of tPERG and ssPERG, respectively.

Specifically, statistically significant differences were found in the P50 amplitudes between normal controls and OHT eyes, with an SMD of −0.59 (95% CI: −1.06 to 0.11; $P = 0.0221$) (Fig 2). The heterogeneity variance among different studies was estimated at $\tau^2 = 0.2$ (95% CI: 0.0 to −1.3) and at $I^2 = 65.5\%$ (95% CI: 26.8%−83.8%) (Fig 2). Interestingly, both the outlier and the influence analysis revealed that the study by Turkey et al[35] majorly impacted the overall heterogeneity of our results, with both the τ^2 and the I^2 statistics dropping to zero when Turkey's data were removed from the pooled analysis (S4).

According to our randomized effect models, the N95 SMD between normal and OHT eyes was −1.44 (95% CI: −2.30 to −0.59; $P = 0.0062$) (Fig 2). A moderate degree of heterogeneity was found among studies with a τ^2 of 0.19 (95% CI: 0.0−2.8) and an $I^2 = 65.8\%$ (95% CI: 10.7%−86.9%) (Fig 2).

While no outliers were found, the influence analysis function in R revealed that data from Elgohary et al greatly impacted the heterogeneity of the pooled results, as shown in the Baujat plot and forest plot reported in Supplementary Material S5.

Furthermore, a subgroup analysis comparing invasive and noninvasive PERG measurement methods did not detect any difference in both the P50 and N95 amplitudes, according to our randomized effect model (S4 and S5).

Regarding ssPERG, an SMD of −1.26 (95% CI: −1.55 to −0.98) was found between normal and OHT eyes in the amplitude of the PERG wave (Fig 2). A moderate level of heterogeneity emerged from the analysis ($\tau^2 = 0.2$ [95% CI: 0.0−1.9]; $I^2 = 69.3\%$ [95% CI: 21.2%−88.0%]). No outliers were found, although the study by Price et al emerged as largely contributing to the overall heterogeneity of the proposed result (S6). Notably, both the τ^2 and the I^2 statistics dropped when Price's data were removed from the pooled analysis (S6). No differences were found in a subanalysis comparing SMD data in eyes in which ssPERG was measured using invasive and noninvasive methods (S6).

The analysis of these data indicates that, despite a substantial amount of heterogeneity, the amplitudes of N95 and ssPERG were > 1 SD lower than what was measured in normal controls, while the P50 amplitude was 0.6 SD higher in normal controls than in OHT eyes. These statistically significant differences exist regardless of the recording strategy and the type of electrode used for PERG measurement.

PERG Data Differences Between Normal and GS Eyes

Eight of the included studies variably reported information regarding PERG data in normal and GS eyes, of which 5 (63%)[33,34,37,41,43] and 3 (27%)[39,44,46] reported it in the context of tPERG and ssPERG, respectively.

For instance, an SMD of −0.25 (95% CI: −0.54 to 0.04) in the P50 amplitude was found between healthy and GS eyes, without any statistically significant difference between the groups (Fig 3). A low heterogeneity level emerged from the analysis: $\tau^2 = 0.2$ (95% CI: 0.0−1.7) and $I^2 = 21.1\%$ (95% CI: 0.0%−87.9%) (Fig 3). While no outliers were found, the influence analysis demonstrated that the study from Elgohary et al majorly impacted the heterogeneity of pooled results, as shown in the Baujat plot and the forest plot reported in S7.

A statistically significant difference in the N95 amplitude was found between healthy and GS eyes with an SMD of −0.43 (95% CI: −0.68 to −0.17; $\tau^2 = 0.2$ [95% CI: 0.0−2.8]; $I^2 = 65.8\%$ [95% CI: 10.7%−86.9%]; $P = 0.0009$) (Fig 3). No outliers were found. The influence analysis revealed that the study from Elgohary et al impacted the heterogeneity level of the pooled results, as shown in S8.

While no differences emerged from the comparison of invasive and noninvasive PERG recording strategies in the context of P50 ($P = 0.0759$) (S7), the N95 SMD expressed higher absolute values when skin-placed electrodes were used ($P = 0.0060$) (S7 and S8).

Concerning the ssPERG amplitude, a statistically significant SMD was found between normal controls and GS eyes (1.21; 95% CI: −1.58 to −0.84; $\tau^2 = 5.03$ [95% CI: 1.22 to > 100]; $I^2 = 96.0\%$ [95% CI: 91.3%−98.1%]; $P < 0.0001$) (Fig 3). The heterogeneity level dropped to zero when the study by Forte et al was removed from the

Table 2. Quality Assessment of Case Series Studies Checklist from National Institute for Health and Clinical Excellence

Study	1	2	3	4	5	6	7	8
Lee et al.[32]	No	Yes	Yes	Yes	No	No	Yes	Yes
Jung et al.[33]	No	Yes	Yes	No	Yes	No	Yes	Yes
Elgohary et al.[34]	No	No	Yes	Yes	Yes	No	Yes	Yes
Turkey et al.[35]	No	Yes	Yes	Yes	Yes	No	No	Yes
Kurysheva et al.[36]	No	Yes	Yes	No	Yes	No	Yes	Yes
Cvenkel et al.[37]	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Park et al.[38]	No	Yes	No	Yes	No	No	No	Yes
Mavilio et al.[39]	No	Yes	Yes	Yes	Yes	No	No	Yes
Uva et al.[40]	No	Yes	No	No	Yes	No	Yes	Yes
Jafarzadehpour et al.[41]	No	Yes	Yes	No	Yes	No	Yes	Yes
Cellini et al.[42]	No	Yes	No	No	Yes	No	No	Yes
Nebbioso et al.[43]	No	No	No	No	Yes	No	Yes	Yes
Forte et al.[44]	No	Yes	Yes	No	Yes	No	Yes	Yes
North et al.[45]	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Sehi et al.[46]	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Falsini et al.[47]	No	Yes	No	Yes	Yes	No	Yes	Yes
Parisi et al.[48]	N/A	Yes	Yes	No	Yes	No	No	Yes
Aldebasi et al.[49]	No	Yes	No	Yes	Yes	No	Yes	Yes
Salgarello et al.[50]	No	Yes	No	Yes	Yes	No	Yes	Yes
Fernandez-Tirado et al.[51]	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Bach et al.[52]	N/A	Yes	No	Yes	Yes	No	Yes	Yes
Bielik et al.[53]	N/A	Yes	No	Yes	Yes	No	Yes	Yes
Price et al.[54]	N/A	Yes	Yes	Yes	Yes	No	Yes	Yes

Quality Assessment of Case Series Studies Checklist from National Institute for Health and Clinical Excellence. ([1] Was the case series collected in > 1 center [i.e., multicenter study]? [2] Is the hypothesis/aim/objective of the study clearly described? [3] Are the inclusion and exclusion criteria [case definition] clearly reported? [4] Is there a clear definition of the outcomes reported? [5] Were data collected prospectively? [6] Is there an explicit statement that patients were recruited consecutively? [7] Are the main findings of the study clearly described? [8] Are outcomes stratified [e.g., by abnormal results, disease stage, patient characteristics]?)

pooled analysis, as it had been identified as an outlier that significantly impacted the heterogeneity level of the results (S9). No subanalysis was performed, as all the included studies were conducted using skin electrodes.

According to our analysis, the ssPERG amplitude measured in GS eyes is 1.2 SD lower than in healthy controls. The directionality and the significance of the outcome persist after the removal of an outlier. No substantial differences emerged between the 2 groups of eyes when the P50 and N95 amplitudes were analyzed.

PERG Data Differences Between Normal and EMG Eyes

Twelve of the included articles reported data comparing PERG data in normal controls and EMG eyes, of which 7[32–34,36,37,41,45] and 5[36,39,47,50,52] were in the context of tPERG and ssPERG, respectively. Because Falsini et al[47] separately reported PERG data from both the right and left eyes of each included participant, we decided to split the study in 2, assuming a biological asymmetry of both the RGC response to the PERG stimulus and of the diseased status.

According to our random-effect model, no difference in the P50 amplitude was detected between the controls and the EMG eyes (SMD: −0.54; 95% CI: −1.36 to 0.27; τ^2 = 0.66 [95% CI: 0.21−3.69]; I^2 = 86.4% [95% CI: 74.1%−92.8%]; P = 0.1533) (Fig 4). The sensitivity analysis revealed that the studies from Elgohoray et al, Kurysheva et al, and North et al greatly impacted the heterogeneity of the pooled analysis (S10). The removal of those studies resulted in the heterogeneity level dropping to 0 and the P50 SMD between the control and the EMG acquiring statistical significance, as reported in S10 (P = 0.0015). Notably, no differences between invasive and noninvasive PERG measuring methods were found (P = 0.5802) (S10).

A statistically significant difference between healthy and EMG eyes emerged in the N95 amplitude, with an SMD of −0.88 (95% CI: −1.52 to −0.24; P = 0.0151) (Fig 4). A high level of heterogeneity emerged from the analysis with a τ^2 = 0.33 (95% CI: 0.72−2.31) and an I^2 = 73.9% (95% CI: 44.1%−87.8%) (Fig 4). A slight reduction in the heterogeneity level was achieved with the removal of outliers from the pooled analysis (S11). Specifically, the studies from Elgohoray et al and Kurysheva et al majorly impacted the heterogeneity of the pooled results. Notably, no differences between invasive and noninvasive PERG measuring methods were found (P = 0.7936) (S11).

In the context of ssPERG, a statistically significant difference in the PERG wave amplitude between normal and EMG eyes was found, with an SMD of −1.78 (95% CI: −2.38 to −1.18) (P = 0.0006) (Fig 4). A moderate level of heterogeneity emerged from the analysis, with the τ^2 = 0.21 (95% CI: 0.00−1.57) and the I^2 = 58.4% (95% CI: 0.0%−83.1%) (Fig 4). While no outlier was found,

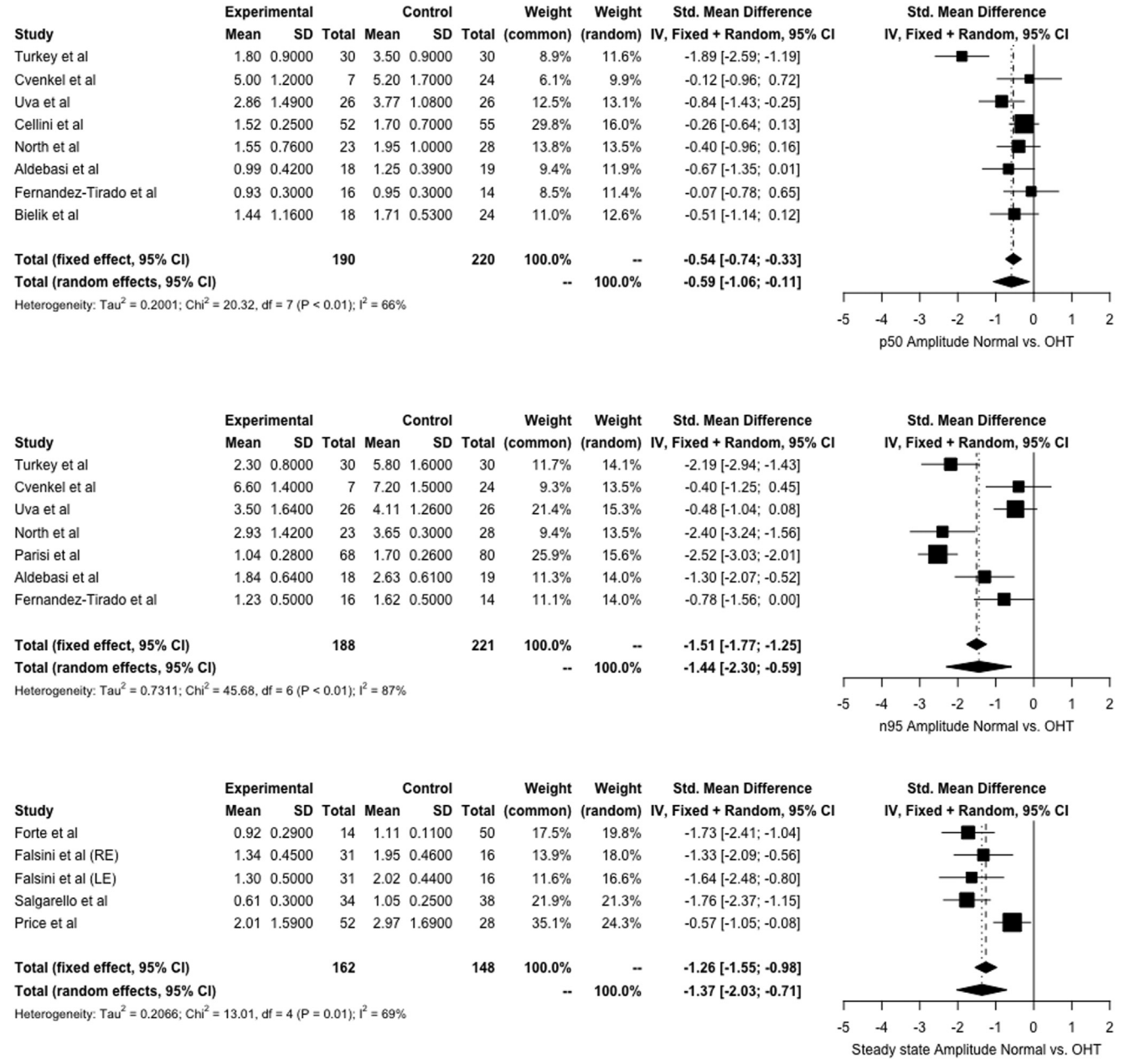

Figure 2. Forest plot showing the standardized mean difference of P50, N95, and steady state pattern electroretiogram amplitude between control and ocular hypertensive eyes. Pooled data were obtained by nonrandomized studies only. CI = confidence interval; IV = inverse variance; OHT= ocular hypertension; SD = standard deviation; Std = standardized.

the influence analysis demonstrated that the study from Mavilio et al exerted a major impact on the overall heterogeneity level (S12). The heterogeneity level dropped to 0 when that study was removed from the pooled analysis, as shown in S12. No difference in the SMD was found when invasive and noninvasive ssPERG recording methods were compared ($P = 0.8102$) (S12).

As per this analysis, in EMG eyes, the N95 and ssPERG amplitudes were 0.88 and 1.78 SD lower than their healthy counterparts, respectively, regardless of the type of electrodes used for the recording. No differences between the 2 groups emerged when the P50 values were compared.

Discussion

In the present study, we aimed to provide the standardized confidence limits of the P50, N95, and ssPERG amplitudes from a population of normal eyes as compared with eyes classified as OHT, GS, or EMG.

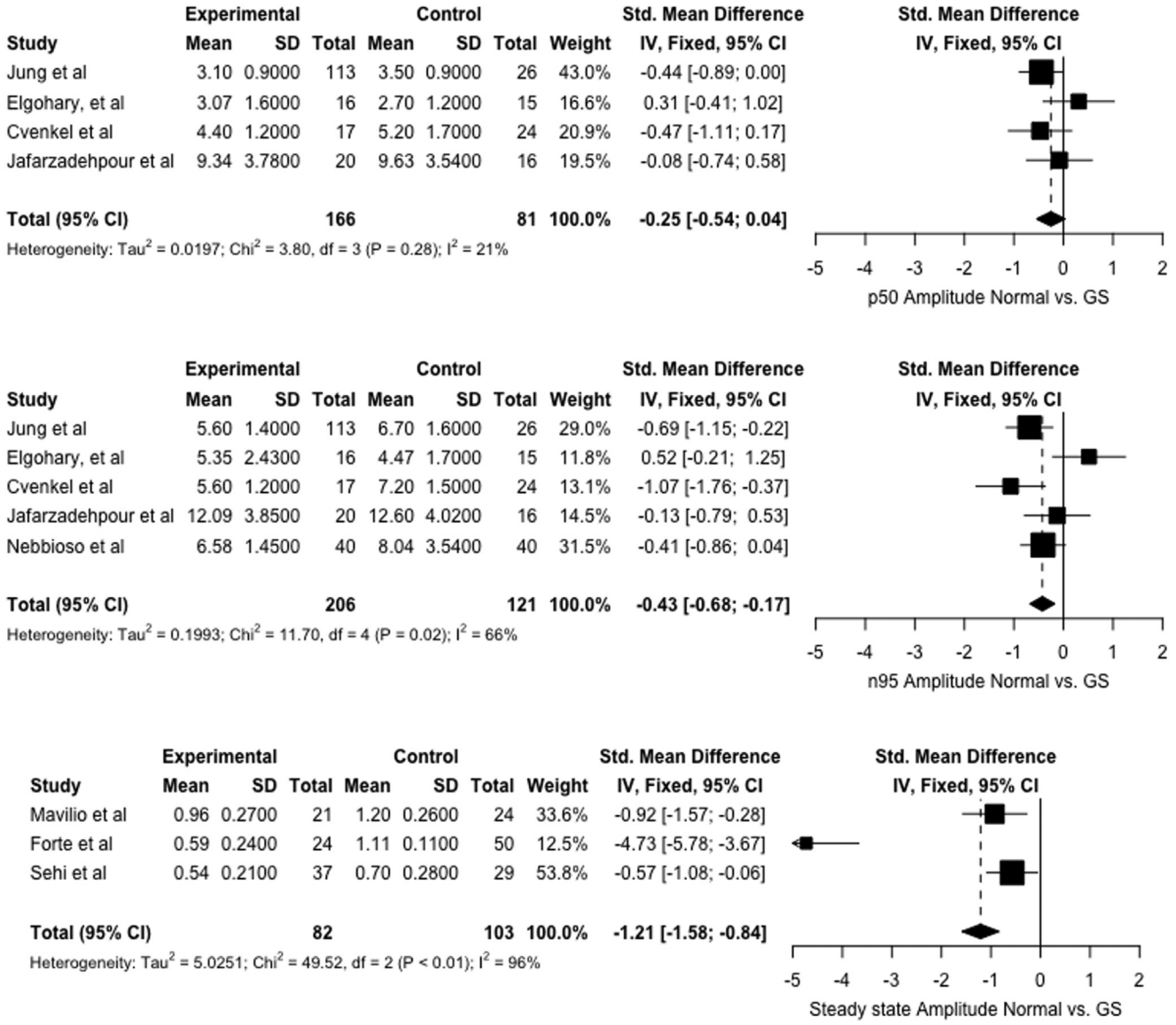

Figure 3. Forest plot showing the standardized mean difference of P50, N95, and steady state pattern electroretinogram amplitude between control and ocular glaucoma suspect (GS) eyes. For all comparisons, a fixed-effect model was chosen, with the number of included studies being ≤ 5. Pooled data were obtained by nonrandomized studies only. CI = confidence interval; IV = inverse variance; SD = standard deviation; Std = standardized.

We decided to use SMD as the preferred effect size measure for its ability to estimate the standardized distance between 2 group means.[20] Pattern electroretinogram recordings feature an intrinsic intralaboratory and interlaboratory variability, due to the variety of permissible PERG recording instruments, settings, and their individual calibration requirements.[1] Hence, referring to nonnormalized measures would have resulted in obtaining unreliable figures.

The demographic and clinical features of our analysis (Table 1) appeared to be similar to those reported in other large population studies, and they are in line with the predefined inclusion and exclusion criteria for this meta-analysis.[56,57] This finding further substantiates our results, depicting them as reliable measures to be adopted in the context of daily clinical practice.

Based on the analysis of 1724 eyes, significant differences were found between control and diseased eyes in the P50, N95, and ssPERG SMD values. Interestingly, the lowest SMD absolute values were observed in the normal versus GS group relative to the other 2 sets of comparison (i.e., normal vs. OHT; normal vs. EMG). While counterintuitively assuming a worsening ocular clinical status in eyes defined as GS rather than OHT, this evidence might be explained by the definition of GS, the clinical features of the GS eyes included in our analysis, and the known impact of high IOP levels on RGC functionality. The GS group is highly heterogeneous, including a large proportion of eyes

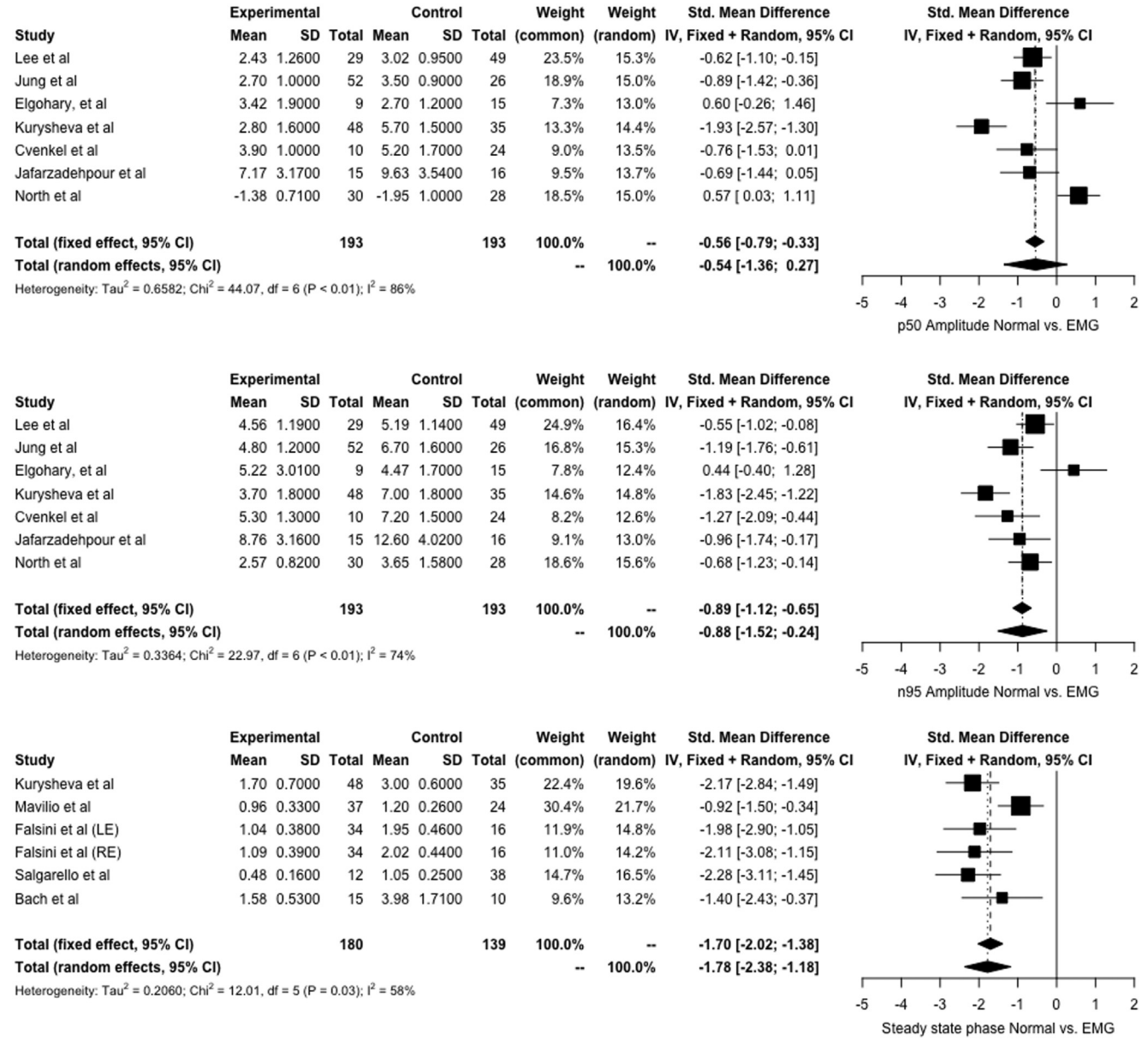

Figure 4. Forest plot showing the standardized mean difference of P50, N95, and steady state pattern electroretinogram amplitude between control and ocular early manifest glaucoma (EMG) eyes. For all comparisons, a randomized effect model was chosen, with the number of included studies being > 5. Pooled data were obtained by nonrandomized studies only. CI = confidence interval; IV = inverse variance; SD = standard deviation; Std = standardized.

which would not progress to frank glaucomatous optic neuropathy.[16,58] In addition, as suggested by international guidelines, GS eyes were included in this study regardless of the actual measured IOP (or of the presence of an IOP lowering therapy).[14,15] Specifically, the mean IOP we observed in the GS group was 17.8 mmHg (95% CI: 15.9−19.6 mmHg), which was lower than that in OHT and EMG eyes (OHT IOP: 17.8 mmHg [95% CI: 15.9−19.6 mmHg]; EMG IOP: 19.9 [15.1−24.8]). Several previous studies have reported the PERG amplitude to be strictly dependent on the IOP level. For instance, in a longitudinal study, Ventura et al[6] reported the progressive loss of RGC function in EMG to be alleviated after IOP lowering. In contrast, the head-down posture, accompanied by an increase in the IOP levels, was shown to determine a reversible reduction in the PERG amplitude.[59] Several factors have been linked to the IOP-dependent RGC dysfunction, such as biomechanically induced strains at the optic nerve head or a variation in the IOP cerebral spinal fluid pressure gradient.[60,61]

In all the comparison sets (i.e., normal vs. OHT, normal vs. GS, and normal vs. EMG), the lowest SMD values were observed in the context of the P50 wave amplitude. This finding appears in line with the supposed physiological

origin of the P50 wave. Specifically, while N95 is believed to be generated by the action potential of RGCs, the source of P50 is still debated; it is supposed to derive from the combined activity of RGCs and some other distal components (e.g., amacrine and bipolar cells). [62−64]

In our subanalysis, we tried to compare the SMDs obtained from PERG data gathered by means of invasive PERG recording methods (e.g., foil, loop, or fiber electrodes) and those obtained using active skin electrodes. In all 3 sets of comparison (i.e., normal vs. OHT, normal vs. GS, and normal vs. EMG), no statistically significant differences emerged between the 2 different approaches, although the SMD absolute values appeared to be higher in the context of noninvasive PERG recording strategies. Interestingly, our data contradict information provided by the International Society for Clinical Electrophysiology of Vision. In the 2012 update of their standard for clinical pattern electroretinography, it is reported that skin (surface) active electrodes should not routinely be used for recording the standard PERG because skin electrodes positioned on the lower eyelid will record PERGs of lower amplitudes than those recorded from an electrode in contact with the eye.[1] Based on our results, skin-active electrodes were able to discriminate healthy and diseased statuses, an observation in line with the currently available literature.[3,4,44,46] Interestingly, Bach et al[8] already proposed skin electrodes as a valid alternative to corneal electrodes, with their advantages being no direct eye contact and a smaller normal amplitude range compared to Dawson−Trick−Litzkow.

The strengths of our meta-analysis include the critical appraisal of study quality, the rigorous application of diagnostic criteria, and the strict observation of inclusion and exclusion criteria. The use of SMD as the main outcome measure and as a proxy for the z-score guarantees a high level of generalizability to the proposed results. Nonetheless, to ensure the highest level of robustness, subgroup analyses, influence analyses, and a sensitivity analysis were conducted. Our study also has limitations inherent to meta-analysis.[65−67] The low number and risk of bias of included studies as well as a certain variability in the inclusion and exclusion criteria in each individual study must be considered in the interpretation of our results (S2). In addition, no metaregression was conducted, given that there were < 10 included articles per each end point. This limitation prevented us from analyzing the impact of external confounders (e.g., age, gender, mean deviation, IOP) on pooled results.

Notably, PERG latency/phase was not analyzed in the present study. While this might represent a limitation, several considerations should be made. First, the PERG latency/phase in glaucoma has been infrequently assessed and has often led to inconsistent results.[5,48,68−70] In addition, standardization of ssPERG phase/latency is not a straightforward process. The determination of ssPERG phase/latency is dependent on a variety of factors, including the pattern reversal frequency, the refresh rate, and the onset time of the pattern reversal.[7] While recent displays with instantaneous refresh, such as LED displays, allow for the conversion of relative phase values into absolute latency values, this is not possible with cathode-ray tube displays, which have frequently been used in the available literature.[7,71] As a result, conducting a precise and reliable analysis based on the available data is currently not feasible.

To the best of our knowledge, this work represents the first systematic review and meta-analysis effectively defining standardized PERG reference values to compare healthy, OHT, GS, and EMG eyes. According to our analysis, SMDs of the ssPERG amplitude were statistically significant in all 3 different sets of comparison (normal vs. OHT, normal vs. GS, and normal vs. EMG), a finding which apparently suggests the ssPERG is able to better discriminate between healthy and diseased eyes. However, no specific conclusion can be drawn regarding the diagnostic capability of the provided SMDs, as we did not analyze the sensitivity, specificity, or receiver operating characteristic parameters. In addition, as there was only 1 study reporting both the tPERG P50-N95 and the ssPERG amplitude data, we were not able to compare statistical differences in the SMD value between the 2 different waveforms.

Nonetheless, as already variably described in the literature, our results further corroborate the PERG as an effective method able to identify early RGC dysfunction, regardless of the methodology adopted for the recording.[4,68,72]

The adoption of the z-score (i.e., SMD) as the main outcome measure in the context of the PERG data analysis seems a valid approach. Acknowledging the high variability as a main defining feature of the PERG, the use of the z-score might help in overcoming the difficulties in comparing and compiling PERG data between different tests, sites, and operators, which has affected the clinical utility of PERG both for individual patients and in clinical trials. Nonetheless, its wide adoption in the literature could lead to a more direct and intuitive understanding of the results, especially if compared to normative reference values.

Further studies are warranted to increase the pool of available data to use for the creation of reference databases as well as to identify the exact role of the PERG in the management of at-risk and EMG glaucoma patients.

Conclusion

As variably reported in the literature, the PERG has been shown to be a promising tool for the early detection of RGC dysfunction, being able to identify an eye at risk 1 year before manifesting glaucomatous field damage.[69] The simplification and standardization of recording protocols as well as the adoption of standardized reporting measures, such as the one we propose, could be helpful tools that may facilitate the adoption of the PERG in routine clinical practice.

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HUMAN SUBJECTS: This systematic review and meta-analysis conformed to the Cochrane Handbook, and results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Since all the reported data were obtained from the available published literature, neither institutional review board approval nor informed consents were required for this study.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Afflitto, Chou, Nucci, Porciatti

Data collection: Afflitto, Chou, Aiello

Analysis and interpretation: Afflitto, Swaminathan, Gedde, Porciatti

Obtained funding: N/A

Overall responsibility: Afflitto, Swaminathan, Gedde, Nucci, Porciatti

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Abbreviations and Acronyms:
C/D = cup-to-disc ratio; **CI** = confidence interval; **EMG** = early manifest glaucoma; **GS** = glaucoma suspect; **IOP** = intraocular pressure; **OHT** = ocular hypertension; **PERG** = pattern electroretinogram; **RGC** = retinal ganglion cell; **SD** = standard deviation; **SMD** = standardized mean difference; **ssPERG** = steady state pattern electroretinogram; **tPERG** = transient pattern electroretinogram.

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