Full-Field Electroretinography Changes Associated with Age-Related Macular Degeneration: A Systematic Review with Meta-Analyses

Thomas Richard Johansen Forshaw^{a, b} Yousif Subhi^{a, b} Sten Andréasson^c
Torben Lykke Sørensen^{a, d}

^aDepartment of Ophthalmology, Zealand University Hospital, Roskilde, Denmark; ^bDepartment of Ophthalmology, Rigshospitalet-Glostrup, Glostrup, Denmark; ^cDepartment of Ophthalmology, Lund University, Lund, Sweden; ^dDepartment of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Keywords

Age-related macular degeneration · Full-field electroretinography · Functional testing · Peripheral retina

Abstract

Background: The aim of this study was to systematically review the literature and to perform meta-analyses on full-field electroretinography (ffERG) between healthy controls and age-related macular degeneration (AMD) to map the extent of retinal dysfunction. **Summary:** We systematically searched 11 databases on 3 March 2021. Eligible studies had to measure retinal function using ffERG in eyes with AMD and in healthy controls. We extracted data on a-wave and b-wave function in dark- and light-adapted ffERG and calculated summary estimates on differences between eyes with AMD and controls using weighted mean differences (WMD). Sub-group analyses were made for early and late AMD. Six studies ($n = 481$ eyes) were eligible for review (301 with any AMD, 180 controls). For dark-adapted data, any AMD was associated with reduced a-wave amplitude (WMD: $-17.16 \mu\text{V}$; 95% CI: -31.79 to $-2.52 \mu\text{V}$; $p = 0.02$) and b-wave amplitude (WMD: $-28.70 \mu\text{V}$; 95% CI: -51.40 to $-6.01 \mu\text{V}$; $p = 0.01$). For light-adapted data, any AMD was associated with longer a-

wave implicit time (WMD: 0.92 ms ; 95% CI: 0.12 – 1.72 ms ; $p = 0.02$), reduced b-wave amplitude (WMD: $-13.26 \mu\text{V}$; 95% CI: -18.64 to $-7.88 \mu\text{V}$; $p < 0.0001$), and longer b-wave implicit time (WMD: 0.69 ms ; 95% CI: 0.30 – 1.08 ms ; $p = 0.0006$). Sub-group analyses found that these changes were only statistically significant in eyes with late AMD, not early AMD. **Key Messages:** Reduced retinal function on ffERG is present in eyes with AMD, in particular those with late AMD. These findings suggest that AMD is a pan-retinal disease with AMD-associated photoreceptor dysfunction beyond the macula.

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Introduction

Age-related macular degeneration (AMD) is the most common cause of irreversible vision loss in the Western World [1]. AMD is often described as a form of exaggerated retinal aging, as even normal aging leads to a decline in retinal function [2]. Hallmarks of early AMD are drusen and changes to the retinal pigment epithelium, characteristics that are thought to be present in 8.0% of individuals aged 45 years or more [1]. Late AMD is further characterized by retinal atrophy and/or neovasculariza-

tion, features that are estimated to be present in 0.4% of the population aged 45 years or more [1]. The impact of AMD on visual function can be severe and near-distance vision is often affected [3]. The disease may result in difficulties reading and problems recognizing faces. AMD is therefore believed to be a disease of the central macula. Despite its name, recent studies are challenging this perception of AMD. OCT-based studies have shown evidence of photoreceptor degeneration in the retinal mid-periphery distant to geographic atrophy boundaries [4, 5], while other studies show evidence of extramacular disease on ultrawide-field imaging, with AMD-like lesions in the peripheral retina that are more prevalent in patients with AMD than in healthy individuals. However, the impact of these peripheral lesions on retinal function is yet to be fully understood [6].

ffERG is a clinical test of overall retinal function that helps in the diagnosis and prognosis of retinal diseases with extramacular manifestations. ffERG can therefore investigate the impact of peripheral retinal lesions leading to a better understanding of overall retinal function in AMD. Modern ERG makes use of the International Society for Clinical Electrophysiology of Vision (ISCEV) standardized protocol that enables the comparison of data from different laboratories around the world [7] and while studies are showing that patients with AMD have an impaired overall retinal response [2], academic and clinical consensus regarding this has yet to be reached. The purpose of our study was therefore to systematically review the literature and perform meta-analyses to map and investigate possible differences in ffERG between patients with AMD and healthy individuals.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [8, 9]. Further, we followed the recommendations of the Cochrane Handbook for all aspects of the study [10]. According to Danish law, Institutional Review Board approval is not relevant for systematic reviews.

Eligibility Criteria

We defined eligible studies as studies measuring ffERG (regardless of method, protocol, or machinery) in a patient group with AMD (regardless of diagnostic methods or disease definition) and in a healthy control group (defined as having a healthy retina as per authors' definition). We did not restrict studies based on study design, geography, or journals. We included relevant abstracts, but not studies without original data or case reports. We only considered studies disseminated in English language.

Information Sources, Search, and Study Selection

We searched the following literature databases: PubMed/MEDLINE, EMBASE, Web of Science Core Collection, BIOSIS Previews, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, Russian Science Citation Index, SciELO Citation Index, and the Cochrane Central. The search was conducted on 3 March 2021. Details of the literature search strategy are available as online supplementary File 1 (see www.karger.com/doi/10.1159/000521834 for all online suppl. material).

One author (T.R.J.F.) examined the title and abstracts from the literature search and removed duplicates and obviously irrelevant reports. Two authors (T.R.J.F. and Y.S.) then examined full text of remaining references for eligibility and reviewed references from these studies for any additional relevant studies. In case of disagreement, a third author (T.L.S.) would be invited to discuss to reach a final decision.

Data Extraction and Risk of Bias Assessment

Data regarding study design, characteristics, methods, and results were extracted from eligible studies using extraction forms. Since we expected most of the studies to be of observational cross-sectional type, quality of eligible studies was assessed using the Agency for Healthcare Research and Quality checklist for Cross-Sectional Studies [11]. Two authors (T.R.J.F. and Y.S.) worked independently on data extraction and risk of bias assessment and met afterwards to compare results and discuss any discrepancies. In case of disagreement, a third author (T.L.S.) would be invited to discuss to reach a final decision.

Outcome Measures, Data Analysis, and Data Synthesis

Our primary outcome measure was a-wave function (amplitudes and implicit times in dark-adapted and light-adapted ERG) as this represents photoreceptor function. Our secondary outcome measure was b-wave function (amplitudes and implicit times in dark-adapted and light-adapted ERG) as this represents inner retinal function, which is coupled with photoreceptor function. These estimates were compared between eyes with any AMD and controls, as well as specifically between early AMD and controls, and late AMD and controls. All studies were qualitatively reviewed and described in text and in tables. Meta-analyses were performed using MetaXL 5.3 (EpiGear International, Sunrise Beach, QLD, Australia) for Microsoft Excel 2013 (Microsoft, Redmont, WA, USA) using the random-effects model. Summary estimates were reported as weighted mean differences (WMD). Due to low number (<5) of eligible studies in meta-analyses, we avoided detailed interpretation of heterogeneity statistics (Cochran's Q and I^2), risk of bias across studies (Funnel plot and Doi plot), and sensitivity analyses (recalculation by excluding studies in turn). Instead, these ancillary analyses are included as online supplementary files. Summary estimates were presented using 95% confidence intervals (95% CI) and p values. p values <0.05 were interpreted as sign of statistical significance.

Results

Study Selection

The literature search identified 585 records and one study known a priori to us was added to the records. Of

Fig. 1. Flow diagram of study selection.

these 586 records, 256 were duplicates and 317 were obviously irrelevant. The remaining 13 records were read in full text. Reviewing reference lists did not identify additional eligible studies. After reading full text, we concluded that six studies were eligible for the qualitative review, of which four were eligible for the quantitative synthesis (Fig. 1).

Study Characteristics

The six studies summarized data on a total of 481 eyes, of which 301 had any AMD and 180 were controls (Ta-

ble 1). All studies provided cross-sectional data from North America ($n = 3$) or Europe ($n = 3$). Data from these studies did not disclose racial distribution of the participants apart from Jackson et al. [14], who reported that 2 patients with early AMD and 3 elderly controls were black. Although the definition of what constitutes AMD did not differ largely across studies, we observed a more pronounced difference in the diagnosis of AMD, the stage of AMD considered eligible, as well as the clinical description of eyes with AMD included in the individual studies.

Table 1. Study characteristics and details of the sample populations

Reference	Country	Study design	Definition of AMD	AMD, N	Characteristics of patients with AMD	Definition of controls	Controls, N	Characteristics of controls
Binns and Margrain [12]	UK	Cross-sectional	Drusen ≥ 63 μ m, focal hyperpigmentation, GA, or CNV. No other fundus abnormalities. BCVA ≤ 0.5 logMAR	31 eyes with any AMD	72.4 $\pm$ 8.0 years 52% females 0.20 $\pm$ 0.15 logMAR	Normal retinal and optic nerve head in both eyes and BCVA of ≤ 0.2 logMAR	27 eyes	71.7 $\pm$ 7.0 years 46% females 0.04 $\pm$ 0.07 logMAR
Dimopoulos et al. [13]	Canada	Cross-sectional	Neovascular AMD in anti-VEGF treatment without any cataract, diabetic retinopathy, glaucoma, ocular hypertension, history of medication with retinal or optic nerve toxicity, optic neuropathy, or history of ocular surgery apart from cataract surgery	20 eyes with dry AMD 18 eyes with wet AMD	Any AMD: 73.6 $\pm$ 8.9 years	Phakic and pseudophakic individuals with BCVA $\geq 20/20$ Snellen, no current or past ocular history and no drusen or fundus pigmentary abnormalities	25 eyes	Phakic controls: 69 $\pm$ 5 years Pseudophakic controls: 71 $\pm$ 4 years
Forshaw et al. [2]	Denmark	Cross-sectional	Early AMD or late AMD (defined as neovascular AMD or GA) confirmed by fundus examination and OCT, without history of other retinal pathology, amblyopia, or glaucoma	12 eyes with early AMD 25 eyes with late AMD	Early AMD: 77 $\pm$ 8 years 42% females 75 $\pm$ 5 ETD Late AMD: 79 $\pm$ 6 years 80% females 53 $\pm$ 32 ETD	Individuals without any vitreoretinal disease	24 eyes	72 $\pm$ 3 years 75% females 76 $\pm$ 10 ETD
Jackson et al. [14]	USA	Cross-sectional	Aged ≥ 60 years and eyes with BCVA 20/80 Snellen. Early AMD: presence of soft distinct or indistinct drusen, drusen ≥ 63 μ m, reticular drusen, or pigment abnormalities. Late AMD: GA or CNV. None had sign of other ocular conditions, refractive error > 6 diopters, neurological conditions, diabetes, or serious frailty or medical conditions expected to lead to mortality or disability < 12 months	39 eyes with early AMD 7 eyes with late AMD	Early AMD: 74.7 $\pm$ 6.0 years 49% females 0.14 $\pm$ 0.17 logMAR Late AMD: 76.4 $\pm$ 10.0 years 43% females 0.27 $\pm$ 0.22 logMAR	Aged ≥ 60 years and eyes with BCVA 20/80 Snellen. Healthy controls* were all defined as those without any drusen or any signs of early or late AMD, or other ocular conditions, refractive error > 6 diopters, neurological conditions, diabetes, or serious frailty or medical conditions expected to lead to mortality or disability < 12 months	41 eyes	70.7 $\pm$ 5.0 years 46% females 0.02 $\pm$ 0.08 logMAR
Ronan et al. [15]	USA	Cross-sectional	Aged ≥ 55 years and AMD diagnosed using color fundus photographs: drusen, GA, or CNV	52 eyes with any AMD	Any AMD: 75.7 $\pm$ 8.6 years 73% females	Elderly healthy ERG controls without any pathologies on color fundus photographs	16 eyes	81.4 $\pm$ 2.3 years 63% females
Walter et al. [16]	Germany	Cross-sectional	Aged > 55 years and eyes with BCVA ≤ 0.625 Snellen. Fundus examination, photographs, and fluorescein angiography were performed. AMD was diagnosed in presence of drusen, pigment epithelium detachment, GA or CNV	32 eyes with early AMD 14 eyes with GA 51 eyes with wet AMD	Any AMD: 70.5 $\pm$ 7.7 years	Aged > 50 years and eyes with BCVA ≥ 0.8 Snellen, no history of eye diseases, no complaints on visual function, refraction ≤ 3 diopters, normal anterior and posterior segments, normal IOP and visual field	47 eyes	66.5 $\pm$ 7.4 years

Data are presented in mean $\pm$ SD where possible. AMD, age-related macular degeneration; CNV, choroidal neovascularization; ETD, Early Treatment of Diabetic Retinopathy Study letters; GA, geographic atrophy; IOP, intraocular pressure; UK, United Kingdom; USA, United States of America; VA, visual acuity; VEGF, vascular endothelial growth factor. *For this review, we did not include data from this study on the separate control group on younger individuals.

Table 2. Study methods for ffERG and reported outcomes

Reference	ffERG methods	Reported ffERG outcomes
Binns and Margrain [12]	DTL electrodes, Fourier analyses used to improve SNR ratio, no mention of ISCEV protocols	ffERG data indirectly reported (ffERG recorded to generate focal-to-full-field amplitude ratios)
Dimopoulos et al. [13]	DTL electrodes, ISCEV standard protocols used	Light-adapted and dark-adapted a- and b-wave amplitudes and implicit times
Forshaw et al. [2]	DTL electrodes, ISCEV standard protocols used	Light-adapted and dark-adapted a- and b-wave amplitudes and implicit times
Jackson et al. [14]	Burian-Allen electrodes, no mention of ISCEV protocols	Rod-mediated a-wave parameters
Ronan et al. [15]	Electrode information not provided, ISCEV standard protocols used	Light-adapted and dark-adapted a- and b-wave amplitudes, implicit times, and maximum stimulation, as well as flicker function
Walter et al. [16]	Contact lens electrodes, ISCEV standard protocols used	Light-adapted and dark-adapted a- and b-wave amplitudes and implicit times, OP2 component of the oscillatory potentials, mean peak-to-peak amplitude of the light-adapted flicker ERG

DTL electrode, Dawson, Trick, and Litzkow electrode; ERG, electroretinography; ffERG, full-field electroretinography; ISCEV, International Society for Clinical Electrophysiology of Vision; OP2, oscillatory potential 2; SNR, signal-to-noise ratio.

Controls were largely well-matched in terms of age and defined broadly across studies as eyes without any vitreo-retinal diseases.

Study methods for ffERG and reported outcomes of individual studies are summarized in Table 2. Four studies (67%) reported to have used the ISCEV standard protocol. Dawson, Trick, and Litzkow electrodes were used in three studies (50%), Burian-Allen electrodes in one study (17%), contact lens electrodes in one study (17%), and no information on electrodes in one study. Four studies (67%) reported light-adapted and dark-adapted a- and b-wave amplitudes and implicit times, and Ronan et al. [15] and Walter et al. [16] also reported flicker function. Binns and Margrain [12] reported ffERG data indirectly through generating focal-to-full-field amplitude ratios. Jackson et al. [14] focused on rod-mediated a-wave parameters.

Results of Individual Studies and Risk of Bias within Studies

Binns and Margrain [12] compared patients with any AMD with an age-matched control group. ffERG responses and focal ERG responses were recorded to determine focal-to-full-field amplitude ratios for each of the two groups. The 5 Hz ERG ratios were not significantly different, but the 41 Hz ERG demonstrated a

focal-to-full-field amplitude ratio in the AMD group that was significantly lower than in the control group [12]. Dimopoulos et al. [13] studied eyes from patients with unilateral wet AMD and fellow-eye dry AMD and compared these results with non-AMD eyes from an age-matched control group. In the dark-adapted responses, there were no significant differences in the amplitudes of the a-wave or b-wave, but implicit times were significantly prolonged throughout all stimulus intensities tested, with implicit times of the a-wave most affected [13]. Further, mean a-wave and b-wave implicit times at maximal stimulus intensity were significantly prolonged in eyes with wet AMD or dry AMD [13]. There were no differences in light-adapted a-wave and b-wave amplitudes and implicit times [13]. Forshaw et al. [2] compared patients with early AMD and patients with late AMD with a healthy control group. There were no differences in the dark-adapted a-wave and b-wave amplitudes and implicit times between the groups, but in the light-adapted responses the 3.0 a-wave implicit times were significantly prolonged in patients with early AMD and late AMD [2]. Thirty Hertz flicker peak times were significantly prolonged in the late AMD group compared to the control group [2]. Jackson et al. [14] compared patients with early AMD and late AMD with a healthy control group. Dark-

Table 3. Risk of bias assessment of individual studies using the Agency for Healthcare Research and Quality checklist for cross-sectional studies

Reference	Defines source	Eligibility criteria	Time period	Consecutive recruitment	Quality assurance	Explains exclusions
Binns and Margrain [12]	Yes	Yes	No	No	Yes	Yes
Dimopoulos et al. [13]	Yes	Yes	No	No	Yes	Yes
Forshaw et al. [2]	Yes	Yes	Yes	Yes	Yes	Yes
Jackson et al. [14]	Yes	Yes	Yes	No	Yes	Yes
Ronan et al. [15]	Yes	Yes	Yes	No	Yes	Yes
Walter et al. [16]	Yes	Yes	No	No	Yes	NR

Studies are assessed Yes/No/Unclear/NR on items from the Agency for Healthcare Research and Quality checklist. Defines source: defines the source of information. Eligibility criteria: lists inclusion and exclusion criteria or refers to previous publications. Time period: indicates time period used for identifying participants. Consecutive recruitment: indicates whether or not subjects were consecutively recruited for the study. Quality assurance: describes any assessments undertaken for quality assurance purposes. Explains exclusions: explains any patient exclusions from analysis. NR, not relevant.

adapted responses were reported, and these did not differ between study groups [14]. Ronan et al. [15] compared patients with any AMD with an age-matched control group. The light-adapted b-wave amplitudes were significantly lower in patients with AMD [15]. Walter et al. [16] compared patients with any AMD with an age-matched control group. Dark-adapted a- and b-wave amplitudes and implicit times were significantly reduced and prolonged when stimulus intensities of 0.1 cd/m² or higher were used [16]. The OP2 component of the oscillatory potentials was significantly reduced in the AMD group, as were light-adapted a- and b-wave amplitudes [16]. Light-adapted a-wave implicit times were significantly prolonged, whereas b-wave implicit times were normal. The mean peak-to-peak amplitude of the flicker ERG was not affected [16]. Furthermore, ffERG across morphological subtypes showed prolonged rod-driven b-wave implicit times in eyes with GA and shorter bright-flash a-wave implicit times in eyes with pigment epithelial detachment compared to other AMD subgroups [16].

Risk of bias evaluation of individual studies showed that source of information, eligibility criteria, quality assurance, and explanation of rationale for any patient exclusion were all declared sufficiently in the six studies. Time period of study was only clearly declared in three studies (50%). Although all studies were performed in a clinical setting with recruitment of patients and healthy controls, only one study (17%) declared that recruitment was made in a consecutive fashion. Details of the risk of bias assessment are available in Table 3.

Synthesis of Results in Meta-Analyses and Risk of Bias across Studies

Four studies were sufficiently homogenous in methods (all ISCEV standard protocols) and outcomes (light-adapted and dark-adapted a- and b-wave amplitudes and implicit times) to allow a meaningful quantitative synthesis [2, 13, 15, 16]. Data on a- and b-wave amplitudes and implicit times were extracted on 3.0 cd s/m² light intensity ffERG test under light-adapted and dark-adapted conditions.

Meta-Analyses of the Differences between Controls and Eyes with AMD in Light-Adapted ffERG Responses

Four studies with data on 276 eyes with AMD and 112 controls provided eligible data for the analyses of light-adapted ffERG data [2, 13, 15, 16]. The random-effects WMD summary estimates are summarized in Table 4. For any AMD, we found significantly longer a-wave implicit time (WMD: 0.92 ms; 95% CI: 0.12–1.72 ms; $p = 0.02$), significantly reduced b-wave amplitude (WMD: $-13.26 \mu\text{V}$; 95% CI: -18.64 to $-7.88 \mu\text{V}$; $p < 0.0001$), and significantly longer b-wave implicit time (WMD: 0.69 ms; 95% CI: 0.30–1.08 ms; $p = 0.0006$). Early AMD was not associated with any significant differences. In late AMD, we found significantly longer a-wave implicit time (WMD: 0.93 ms; 95% CI: 0.21–1.66 ms; $p = 0.01$), significantly reduced b-wave amplitude (WMD: $-17.43 \mu\text{V}$; 95% CI: -23.50 to $-11.35 \mu\text{V}$; $p < 0.0001$), and significantly longer b-wave implicit time (WMD: 1.01 ms; 95% CI: 0.56–1.47 ms; $p < 0.0001$). Detailed results of individ-

Table 4. Random-effects WMD summary estimates of the light-adapted ffERG responses in eyes with any AMD, early AMD, or late AMD, all in comparison to healthy controls

Study sample	ffERG test	WMD	95% CI	p value
Any AMD versus healthy control	a-wave amplitude	−3.59 μ V	−9.36 to 2.18 μ V	0.2
	a-wave implicit time	0.92 ms	0.12–1.72 ms	0.02
	b-wave amplitude	−13.26 μ V	−18.64 to −7.88 μ V	<0.0001
	b-wave implicit time	0.69 ms	0.30–1.08 ms	0.0006
Early AMD versus healthy control	a-wave amplitude	−0.76 μ V	−5.46 to 3.94 μ V	0.8
	a-wave implicit time	0.78 ms	−1.34 to 2.91 ms	0.5
	b-wave amplitude	−10.99 μ V	−22.58 to 0.60 μ V	0.06
	b-wave implicit time	0.59 ms	−0.28 to 1.46 ms	0.2
Late AMD versus healthy control	a-wave amplitude	−4.66 μ V	−12.02 to 2.70 μ V	0.2
	a-wave implicit time	0.93 ms	0.21–1.66 ms	0.01
	b-wave amplitude	−17.43 μ V	−23.50 to −11.35 μ V	<0.0001
	b-wave implicit time	1.01 ms	0.56–1.47 ms	<0.0001

AMD, age-related macular degeneration; 95% CI, 95% confidence interval; ffERG, full-field electroretinography; μ V, microvolt; ms, millisecond; WMD, weighted mean difference.

Table 5. Random-effects WMD summary estimates of the dark-adapted ffERG responses in eyes with any AMD, early AMD, or late AMD, all in comparison to healthy controls

Study sample	ffERG test	WMD	95% CI	p value
Any AMD versus healthy control	a-wave amplitude	−17.16 μ V	−31.79 to −2.52 μ V	0.02
	a-wave implicit time	5.44 ms	−4.21 to 15.09 ms	0.3
	b-wave amplitude	−28.70 μ V	−51.40 to −6.01 μ V	0.01
	b-wave implicit time	2.38 ms	−2.53 to 7.29 ms	0.3
Early AMD versus healthy control	a-wave amplitude	−3.57 μ V	−21.22 to 14.08 μ V	0.7
	a-wave implicit time	5.52 ms	−4.33 to 15.36 ms	0.3
	b-wave amplitude	11.10 μ V	−20.55 to 42.74 μ V	0.5
	b-wave implicit time	−0.01 ms	−0.26 to 0.25 ms	1.0
Late AMD versus healthy control	a-wave amplitude	−23.39 μ V	−40.02 to −6.77 μ V	0.006
	a-wave implicit time	5.35 ms	−4.20 to 14.89 ms	0.3
	b-wave amplitude	−27.25 μ V	−50.81 to −3.69 μ V	0.02
	b-wave implicit time	0.00 ms	−0.62 to 0.62 ms	1.0

AMD, age-related macular degeneration; 95% CI, 95% confidence interval; ffERG, full-field electroretinography; μ V, microvolt; ms, millisecond; WMD, weighted mean difference.

ual meta-analyses are summarized in online supplementary File 2 with specific heterogeneity statistics, sensitivity analyses, and risk of bias across studies.

Meta-Analyses of the Differences between Controls and Eyes with AMD in Dark-Adapted ffERG Responses

Four studies with data on 238 eyes with AMD and 87 controls provided eligible data for the analyses of dark-adapted ffERG data [2, 13, 15, 16]. The random-effects

WMD summary estimates are summarized in Table 5. For any AMD, we found significantly reduced a-wave amplitude (WMD: −17.16 μ V; 95% CI: −31.79 to −2.52 μ V; p = 0.02) and significantly reduced b-wave amplitude (WMD: −28.70 μ V; 95% CI: −51.40 to −6.01 μ V; p = 0.01). Early AMD was not associated with any significant differences. In late AMD, we found significantly reduced a-wave amplitude (WMD: −23.39 μ V; 95% CI: −40.02 to −6.77 μ V; p = 0.006) and significantly reduced b-wave amplitude (WMD: −27.25 μ V; 95% CI: −50.81 to −3.69 μ V; p = 0.01). Detailed

results of individual meta-analyses are summarized in online supplementary File 3 with specific heterogeneity statistics, sensitivity analyses, and risk of bias across studies.

Discussion

In this systematic review of six studies with 481 eyes, we summarized reported findings and performed meta-analyses on ffERG in AMD. In patients with any AMD, light-adapted 3.0 a-wave implicit times representing cone function were prolonged and light-adapted 3.0 b-wave parameters representing on- and off-bipolar cell function were impaired. Dark-adapted 3.0 a- and b-wave amplitudes representing mixed photoreceptor and post-receptor on-pathway function were also significantly reduced. Patients with early AMD did not differ significantly from healthy controls in terms of their general retinal function, but those with late AMD were found to have significantly worse retinal function in terms of impaired cone system function and impaired rod and dark-adapted cone function when compared with individuals with healthy retina.

Rods are affected earliest and most severely by AMD and are therefore especially vulnerable to the effects of the disease process [17]. As early as 1999, Walter et al. [16] noted that ffERG indicated a global reduction of retinal function in AMD that seemed to be present not only in the macula, but also elsewhere in the retina. The results of our meta-analyses showed evidence of rod dysfunction in patients with late AMD but not in those patients with early AMD when compared with healthy age-matched individuals. This may be because the retina has a relative surplus of rods, or perhaps because AMD shows a predilection for the rods in the parafoveal regions [17, 18]. Unlike patients with rod-cone dystrophies in whom the much larger retinal periphery may be affected from an early stage, the rod dysfunction in AMD may not be observable on ffERG until the disease has entered its late stage, progressing beyond the macula [2, 19]. Jackson et al. [14] have already shown this to be the case, demonstrating that the activation of the a-wave as measured by the rod-mediated ffERG is not affected by early AMD, nor is it impacted by normal retinal aging. Dimopoulos et al. [13] further support this idea, demonstrating that patients that have progressed to unilateral wet AMD have rod dysfunction in both eyes.

The results of our meta-analyses also showed evidence of cone dysfunction in AMD. Ninety percent of cones lie outside the macula [20], and although the photoreceptor subtype is more resilient to the effects of AMD than rods, ffERG shows evidence of cone dysfunction beyond the macula in

patients with the late AMD phenotype and in patients with any AMD, or mixed type. Indeed, Binns and Margrain [12] were able to observe a marked effect on the kinetics of cone adaptation even in patients with early AMD and Forshaw et al. [2] also found an impaired overall cone response, particularly when AMD has reached its later stages [12]. Furthermore, Ronan et al. [15] conclude that a subgroup of patients with AMD with a pan-retinal cone dysfunction exists and that ffERG and genotype tests are likely to be helpful in identifying patients that belong to this subgroup.

A strength of this study is that all four individual studies included in the meta-analyses used the ISCEV standard protocol. The data from these studies were therefore comparable, allowing these methods of analysis to be undertaken. Limitations of this study should be considered. We considered only studies disseminated in English language for practical reasons. Also, the nature of any systematic review and meta-analysis is that it can only consider published studies. Publication bias due to negative results has important implications as to which data are available for analysis, and the small number of eligible studies made it difficult to conclude on risk of bias across studies. It is also important to remember that the different corneal electrodes used in the studies can contribute to a variation of results: although implicit times produced by different types of electrode tend to be comparable, contact lens electrodes can produce higher amplitudes when compared with Dawson, Trick, and Litzkow electrodes [7]. Moreover, an important limitation is that our meta-analysis was based on group means and variations, but not individual participant data (IPD). IPD meta-analyses allow further exploratory options and more accurate estimates of when and how these associations are present. With ongoing focus on data sharing statements and encouragement of the publication of study data, such IPD meta-analyses may allow more detailed analyses. Indeed, comparing the means of ffERG measures between groups does not take into account the clinical heterogeneity that exists within the group of eyes with AMD, and although the results of our meta-analyses were statistically significant, a difference in implicit time of 1 ms or less between AMD and healthy retina is small enough so as not to be applicable to individual patients in clinic. While some eyes with AMD have morphological changes that are strictly central and do not involve the peripheral retina, other eyes show changes that extend well beyond the central macula [6]. One clinical feature that emphasizes this heterogeneity is reticular pseudodrusen, subretinal drusenoid deposits often extending beyond the central macula that are present in some eyes with AMD. Using ffERG, Luu et al. [21] re-

ported that reticular pseudodrusen was associated with severe rod dysfunction. These findings highlight the importance in acknowledging the heterogeneity underlying what we consider to be a single disease entity, which may in fact be a cluster of many different conditions. Semantic considerations suggest that some cases of AMD are better described by the term *age-related retinal dysfunction*. Further studies are therefore warranted that explore the heterogeneity of AMD using fERG.

Conclusion

In conclusion, the global impairment of retinal function found on fERG shows that AMD in an important number of eyes may be a pan-retinal disease that is not confined to the macula alone, especially when it has reached its later stages.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

T.R.J.F and Y.S. searched the literature. T.R.J.F., Y.S., and T.L.S. determined study eligibility. T.R.J.F. and Y.S. extracted the data. Y.S. performed statistical analyses. All authors analyzed and interpreted the data and were major contributors in writing the manuscript. All authors read and approved the final manuscript.