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ORIGINAL PAPER

30 Hz-flicker mfERG in primary open-angle glaucoma patients

30 Hz-flicker-mfERG in POAG

Margarita G. Todorova · Anja M. Palmowski-Wolfe · Selim Orguel · Josef Flammer

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Abstract
Purpose This study was performed in an attempt to gain more information on whether the 30 Hz-flicker mfERG indeed provides a sensitive measure of dysfunction in patients with primary open-angle glaucoma (POAG) as has been suggested previously.
Methods Eighteen POAG patients with visual field defects (MD > 2.2 dB) and glaucomatous optic neuropathies as well as 10 control subjects underwent mfERG recording as follows: 30 Hz-flicker mfERG, LED stimulus screen, 61 hexagons, L_{max}: 180 cd/m^2, L_{min}: 0 cd/m^2, recording time: ~5 min, filter setting: 10–200 Hz. The 30 Hz response (also called the fundamental or the first harmonic response (1HW) and the second harmonic wave at 60 Hz (2HW) were analysed as an overall response and in quadrants, as well as in 4 small neighbouring areas per quadrant. The patients' mfERGs were compared to those of the control group and to the mean defect values (MD) of the corresponding quadrants of the Octopus perimetry.
Results Neither in the overall response, nor in the quadrants, nor in the smaller areas examined did amplitudes and phases of the 1HW and the 2HW or the amplitude ratio of the 2HW to the 1HW (DFT-ratio) differ from the controls ($P > 0.05$—ANOVA). There was no significant correlation between mfERG values and the MD (Spearman-test, Bonferroni).
Conclusion Thus, the 30 Hz-flicker mfERG does not seem to be sensitive enough to separate glaucoma patients from normal.

Keywords Base wave · First harmonic wave · 30 Hz-flicker mfERG · LED-stimulus screen

Abbreviations

1HW	the first harmonic wave at 30 Hz = fundamental wave
2HW	the second harmonic wave at 60 Hz
DFT-ratio	Discrete Fourier Transform-ratio = the amplitude ratio between the 2HW and the 1HW
MD	mean defect of the Octopus perimetry
LED- screen	Light-emitting-diode-screen
SD	standard deviation

M. G. Todorova · A. M. Palmowski-Wolfe (✉) · S. Orguel · J. Flammer
Department of Ophthamlology, University Eye Hospital Basel, Mittlere Strasse 91, CH-4012 Basel, Switzerland
e-mail: palmowskia@uhbs.ch

Introduction

According to the new report of the World Health Organization, glaucoma is the second leading cause of blindness world-wide [1].

Primary open angle glaucoma (POAG) is a progressive optic neuropathy. In early stages it affects the proximal retinal activity, namely the ganglion cells [2]. Static perimetry has been used for years in the clinical diagnosis of glaucoma although the results of the examination are subjectively dependent on the patient. Thus, attempts have been made to find an objective method for routine use in early detection and mapping of glaucomatous dysfunction.

Since the development of the mfERG by Sutter and Tran in 1992 [3] it proved to be an objective method for topographical evaluation of retinal function [4–7]. Previous studies on the mfERG recorded with the VERIS technique reported promising results with increasing sensitivity in the detection of glaucomatous damage [8–13].

Recent studies on glaucoma patients using a 30 Herz-flicker mfERG stimulation generated on a light-emitting diode-monitor (LED) suggested this test to be sensitive enough to separate glaucoma patients from normals [14]. Other studies also reported the 30 Hz-flicker ERG to be an objective test to detect early glaucomatous dysfunction by means of the amplitude ratio of the response at 60 Hz to the response at 30 Hz (DFT-ratio) [15, 16]. There seems to be some confusion in the literature as to the nomenclature of these response components [14–18]. In order to clarify this: the fundamental response is defined as the first harmonic, in this case, the response to a 30 Hz flicker, found at 30 Hz. The second harmonic is then found at 60 Hz (twice the frequency of the first harmonic).

A LED stimulus screen (RETIscan^{TM}, Roland Consult) gives an opportunity of steady luminance for the duration of each stimulus frame. This mfERG system also allows a multifocal 30 Hz-flicker stimulation.

As 30 Hz-flicker stimulation is generally thought to test the cone response [19], our attempt was to gain more information on whether the 30 Hz-flicker mfERG with a LED-monitor indeed provides a sensitive measure of dysfunction in patients with primary open-angle glaucoma (POAG), where dysfunction is to be expected to affect the ganglion cells first [2].

Methods

Subjects

According to the declaration of Helsinki, the study was approved by the Ethics Committee of the University of Basel. A written informed consent was signed from all participants before the commencement of the examination.

Ten control subjects and 18 glaucoma patients were included in the study.

All POAG patients fulfilled the following inclusion criteria: primary open angle glaucoma with best corrected visual acuity >0.79, glaucomatous optic neuropathy with a cup/disc ratio >0.49, long-standing glaucomatous visual field loss detected on Octopus static perimetry (G2 program). All patients had controlled intra ocular pressure (IOP) under 21 mmHg at the time of examination.

Exclusion criteria were hyperopia or myopia greater than 6D and any ocular pathology other than POAG, as well as previous ocular surgery.

The control subjects were healthy volunteers. Exclusion criteria were hyperopia or myopia greater than 6D and any ocular pathology, as well as previous ocular surgery.

Neither subjects nor patients suffered from systemic diseases that might affect mfERG recordings, such as diabetes or hypertension.

The left eye of each patient was recorded, unless exclusion criteria prohibited its examination.

In such case, if the right eye satisfied the inclusion criteria, it was evaluated instead (4 eyes).

For the normal mfERG there seems to be a trend for amplitudes to decline and latencies to increase with age [20–22]. We therefore excluded the two youngest subjects as they were considerably younger than the mean age (30 years, 33 years).

The remaining control group consisted of 8 controls aged 40–76 years (mean age 57.75, SD 10.01). Their best corrected Snellen visual acuity at distance was >0.9, with a refraction ranging between +1.75D and –3.0D. An ophthalmological examination (slitlamp, ophthalmoscopy) showed clear media, a normal appearing optic disc (cup/disc ratio < 0.5) and retina.

The POAG group consisted of 18 patients with a mean age of 58.28 (SD 9.56), a best corrected Snellen visual acuity of >0.79, with a refraction between +3.5 and –5.25D. All glaucoma patients had a glaucomatous optic neuropathy with a cup/disc ratio >0.49 (mean 0.7, (SD 0.13)). Intraocular pressure was controlled by eye drops in 14 patients. Among all patients, the mean intraocular pressure at the time of examination was below 21 mmHg: (mean 14.31 mmHg, SD 2.59). On Octopus perimetry (G2 program) the mean defect (MD) was 6.01 dB (SD 4.87).

30 Hz-flicker mfERG

Patients were adaptated to ambient room light for 30 min.

Pupils were maximally dilated using Tropicamide 0.5% and Phenylephrin 1% eye drops. The cornea was anesthesized using Proxymetacain Hydrochlorid 1%. The skin on the subject's forehead was cleaned with an abrasive cream (Every) and an electrode cream (Ec2, Astro Med, Inc.) was used to adhere the neutral ground electrode to the skin of the forehead. A bipolar gold contact lens electrode (Diagnosys LLC) was wetted with a drop of synthetic carbomer (Thilo-Tears SE^{R}) and placed on the anesthesized cornea. The opposite eye was occluded to avoid blinking.

The stimulation was generated on a light-emitting diode (LED) stimulus screen (RETIscan^{TM}, Roland Consult system). Each LED had a peak wavelength of about 424 nm and a half width of 28 nm. There was a second smaller peak at about 550 nm with a relative luminous intensity of 40% and a half width (at 20% relative luminous intensity) of 120 nm. The temporal stimulus pattern of the 30 Hz mfERG was sinusoidally modulated.

The stimulus array consisted of 1024 (32×32) white light emitting diodes displayed in a stimulus matrix of 61 flickering hexagons. Viewing distance was 28 cm. A corrective lens was not applied. The hexagons stimulated approximately the central 56° of the retina. Five red LED elements in the middle served as a fixation cross. In order to try and take into account the cone distribution within the central retina [23], hexagons were scaled with eccentricity (1:4). Thus, the most peripheral hexagons consisted of 16 LEDs and were four times larger than the central hexagon which consisted of 4 LEDs.

Each hexagon flickered at around 30 Hz with a slightly different frequency between the neighbouring hexagons, ranging from 29.14 Hz to 30.89 Hz. This slight shift in frequency is essential in order to be able and independently extract responses from individual hexagons through a Fourier analysis.

During the light phase the luminance of the hexagons was 180 cd/m^2 and during a dark phase 0 cd/m^2 (100% contrast, mean luminance 90 cd/m^2). Each patient was tested once. Recording time was approximately 5 min, separated into 8 cycles of 39 s duration. Data was sampled at a frequency of 2 kHz. Retinal signals were band-pass filtered: 10–200 Hz.

The Fourier transform has been recommended as a useful tool for the interpretation of steady-state recordings [24]. With the Fourier analysis included in the RETIscan^{TM} software we analysed the first harmonic (1HW) at 30 Hz, also known as the fundamental component, and the second harmonic wave (2HW) at 60 Hz.

We analysed the overall response (OV) as well as the response averages from the superior-nasal (SN), inferior-nasal (IN), inferior-temporal (IT) and superior-temporal (ST) quadrants. Figure 1a depicts a typical response array for a glaucoma patient and a control subject. For the flicker mfERG more peripheral areas within the central 60° have been reported to be more sensitive to detect glaucomatous dysfunction [14]. Therefore, in order to examine the more peripheral retinal sensitivity in each quadrant we averaged the local responses from 4 neighbouring hexagons from the more peripheral retinal areas, without overlapping them. Figure 1b shows the grouping for

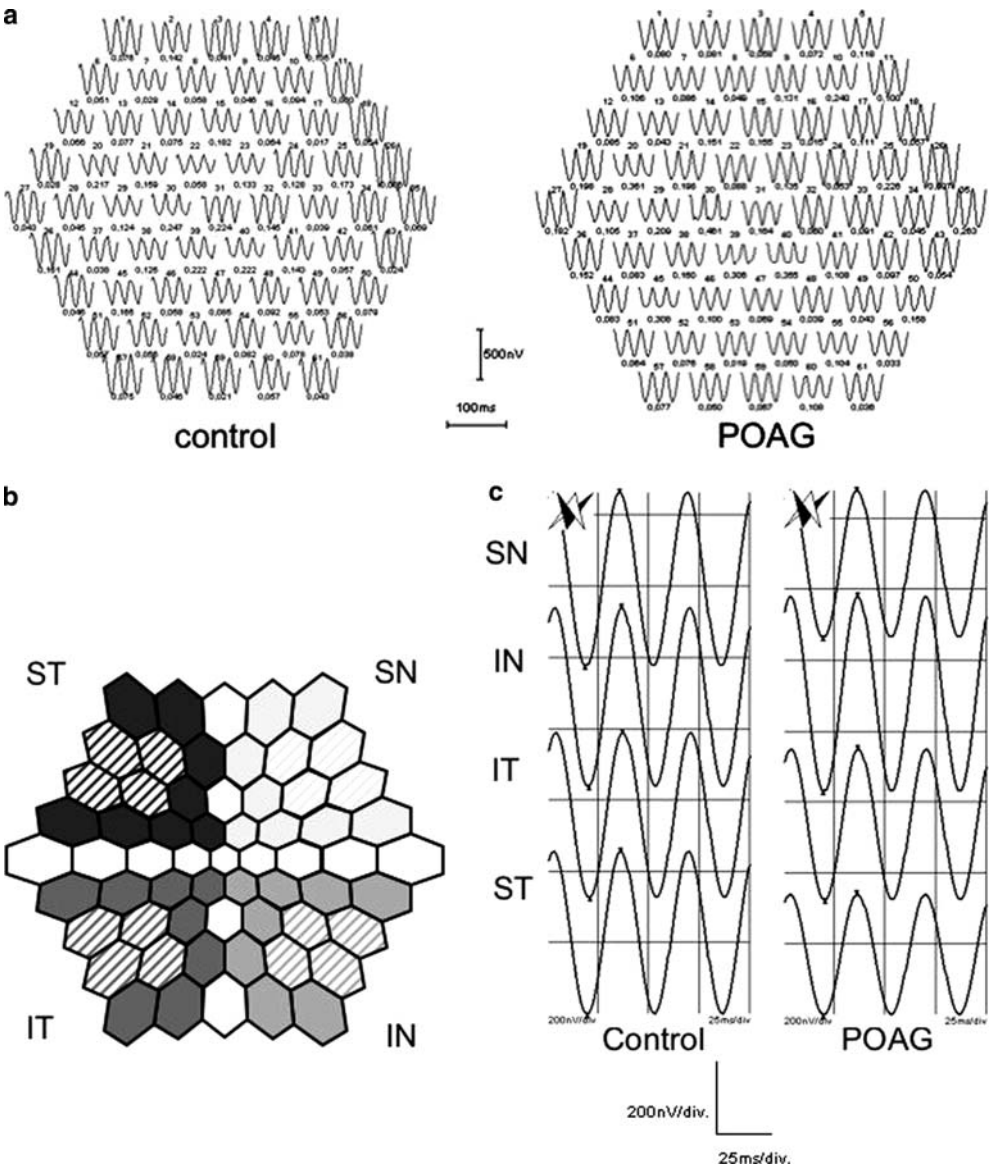

Fig. 1 (**a**) The response arrays from a representative POAG patient with a mean defect of the visual field of 17.9 dB and LV of 45.6 (right) and an age-matched control (left). A DFT-ratio for each one of all 61 traces is presented below the trace arrays. Numbers above the traces depict the hexagon count. (**b**) The areas over which responses were averaged for the response average of the superior-nasal (SN), inferior-nasal (IN), inferior-temporal (IT) and superior-temporal (ST) quadrant. Hexagons in stripes represent responses calculated from 4 neighbouring hexagons of each quadrant from the peripheral retina. (**c**) Representative response averages for the 1HW of the 30 Hz mfERG of a single control (left) and a POAG patient (right)

responses averaged in quadrants (left eye). Hexagons marked in stripes depict the grouping for responses in smaller peripheral areas. MfERG data of POAG patients were compared to control subjects.

Visual field testing

All POAG patients also underwent an Octopus (G2) visual field examination (Octopus model 101, Haag-Streit AG, Switzerland), where 73 locations

within a field of 60° diameter were tested. In addition to the mfERG analysis, we examined the relationship between the mfERG values and the MD values of the corresponding quadrants of the Octopus static perimetry program G2.

Results

Analysis of the overall response

For POAG and the control group Fig. 2 shows the box plots of the resulting amplitudes of the 1HW and the 2HW [nV/deg^2], their corresponding phases [degree] and the ratio between the 2HW- and 1HW-amplitudes, the so called DFT-ratio.

No statistically significant difference was found for the amplitudes between the control group and the POAG-group (one-way ANOVA, $P > 0.05$). For instance, the mean overall 1HW amplitude was 11.78 nV/deg^2 (SD 3.72) in control subjects and 13.25 nV/deg^2 (SD 6.92) in glaucoma patients ($P = 0.58$). The mean overall 2HW amplitude was 0.71 nV/deg^2 (SD 0.35) in the control group and 0.96 nV/deg^2 (SD 0.62) in the glaucoma group ($P = 0.43$).

Phases also did not differ between both groups (one-way ANOVA, $P > 0.05$). The mean overall 1HW phase was 31.25° (SD 13.87) in the control group and 35.46° (SD 17.19) in glaucoma patients ($P = 0.55$). The mean overall 2HW phase was 100.38° (SD 149.47) in the control group and 114.28° (SD 133.75) in the glaucoma group ($P = 0.82$). The mean DFT-ratio was 0.061 (SD 0.02) in the control group and 0.067 (SD 0.03) in the glaucoma group ($P = 0.657$, power: 0.07).

Analysis of responses in quadrants

In the conventional mfERG naso-temporal asymmetry has been reported to be reduced in Glaucoma [8]. In order to test for differences in the naso-temporal asymmetry we averaged responses in quadrants. Figure 1c shows representative group average responses of the 1HW from a single control and a POAG patient.

Table 1 gives the mean responses and the standard deviations (SD) of the 1HW- and the 2HW-phases. Figure 3 depicts the results of the 1HW- and the 2HW-amplitudes and their corresponding DFT-ratio for the quadrants analysed. For statistical analysis, a repeated measure ANOVA (post-hoc: Bonferroni) was performed allowing for correlation between locations and adjusted for age. Glaucoma patients did not differ significantly from the control in either amplitudes of the 1HW ($P = 0.54$), the 2HW ($P = 0.51$) or the phases of the 1HW ($P = 0.21$) and 2 HW ($P = 0.46$) or the DFT-ratio ($P = 0.98$) (Table 2). Although the 2HW amplitude and the DFT-ratio appears to be slightly smaller in the nasal quadrants when compared to the corresponding temporal quadrants (Fig. 3a, b), this difference did not reach significance for either control subjects, nor for POAG patients ($P > 0.05$, one-way ANOVA, Bonferroni). Naso-temporal asymmetry did not differ between the groups: There was no significant influence of location for either the amplitudes of the 1HW ($P = 0.13$), 2HW ($P = 0.74$), or the phases of the 1HW ($P = 0.17$) and 2HW ($P = 0.36$), or for the DFT-ratio ($P = 0.41$) (repeated measure ANOVA (Huynth-Feldt, $P < 0.05$)). When age was taken into consideration, there was also no

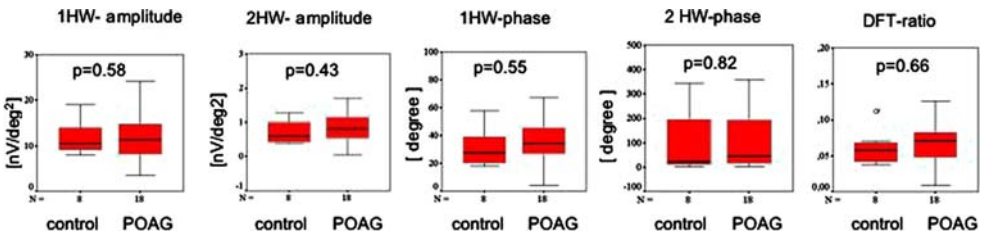

Fig. 2 For the overall response, the box plots depict from left to right: the amplitudes of the 1HW, the amplitudes of the 2HW, the phases of the 1HW, the phases of the 2HW and the DFT-ratio. The box length is the interquartile range, the line in bold depicts the median. In each graph, the control group is plotted to the left and the POAG group is plotted to the right. The respective *P*-value is shown above the graphs (one way ANOVA)

Table 1 1HW- and 2HW-phases in quadrants

		SN Mean Standard deviation	IN Mean Standard deviation	IT Mean Standard deviation	ST Mean Standard deviation
1HW Phases in degrees	Controls	20.93 SD 14.23	32.29 SD 15.51	43.00 SD 13.23	29.69 SD 12.67
	POAG	46.69 SD 78.31	38.1 SD 17.25	45.76 SD 19.73	33.87 SD 16.98
2HW Phases in degrees	Controls	298.13 SD 95.52	41.88 SD 35.06	72.00 SD 146.01	178.80 SD 176.39
	POAG	214.11 SD 145.37	86.33 SD 77.92	71.83 SD 73.59	135.00 SD 148.56

The mean response and it's standard deviation for responses averaged over quadrants for the 1HW phases and the 2HW phases. There was no statistically significant difference between patients and the control group (repeated measure ANOVA, Bonferroni) allowing for correlation between locations and adjusted for age

statistically significant difference between the groups ($P > 0.05$).

Analysis of responses from 4 neighbouring hexagons from the periphery of each quadrant

Again, there was no statistically significant difference between glaucoma patients and the control group for the 1HW ($P = 0.52$) and the 2HW ($P = 0.47$) amplitudes or for the 1HW (0.07), the 2HW phases (0.28) or the DFT-ratio ($P = 0.55$) (repeated measure ANOVA, Bonferroni). The influence of location showed also no significant difference ($P > 0.05$) either for amplitudes of the 1HW ($P = 0.06$), the 2HW ($P = 0.42$), the phases of the 1HW ($P = 0.19$), the 2HW ($P = 0.88$), or the DFT-ratio ($P = 0.27$). There was also no influence of age on these mfERG parameters ($P > 0.05$) (Table 2).

Analyses of visual field parameters

To examine the relationship between mfERG values and the visual field loss (MD) in the glaucoma group we used the Spearman bivariate test. The MD value given in the Octopus perimetry is not only a logarithmic value, but it is also adjusted for age. As a curvilinear relationship between visual field data in dB and linear values of ERG amplitudes has been reported [10], mfERG values were converted to log units (Lg10), and adjusted to mean age (analysis of covariance) before correlating them with the respective mean defect of the Octopus perimetry.

When the age adjusted log mfERG values were compared to the visual field MD values of the corresponding quadrant we could not find a significant correlation for either the 1HW-amplitudes, the 1HW-phases or the DFT-ratio. The highest correlations with a P-value < 0.05 were the following: The MD of the ST quadrant correlated negatively with the 2HW amplitude ($r = -0.529$, $P = 0.02$). Phases of the 2HW correlated positively with the MD in the SN quadrant ($r = 0.630$, $P = 0.01$). Adjusting for multiple testing (Bonferroni), a P-value would be considered significant only if ≤ 0.0025. When the smaller mfERG areas from the periphery of each quadrant were correlated to the MD of the respective quadrants there was still no significant difference between glaucoma patients and the control group (Spearman, Bonferroni).

Discussion

High contrast 30-Hz mfERG recordings with a LED-stimulus screen were obtained from 18 POAG patients and compared to those of 8 healthy volunteers.

The present study could not confirm previous findings that suggested the 30 Hz-flicker mfERG to be a sensitive test to separate glaucoma patients from controls by means of the response at 60 Hz and the DFT-ratio [14]. There was no

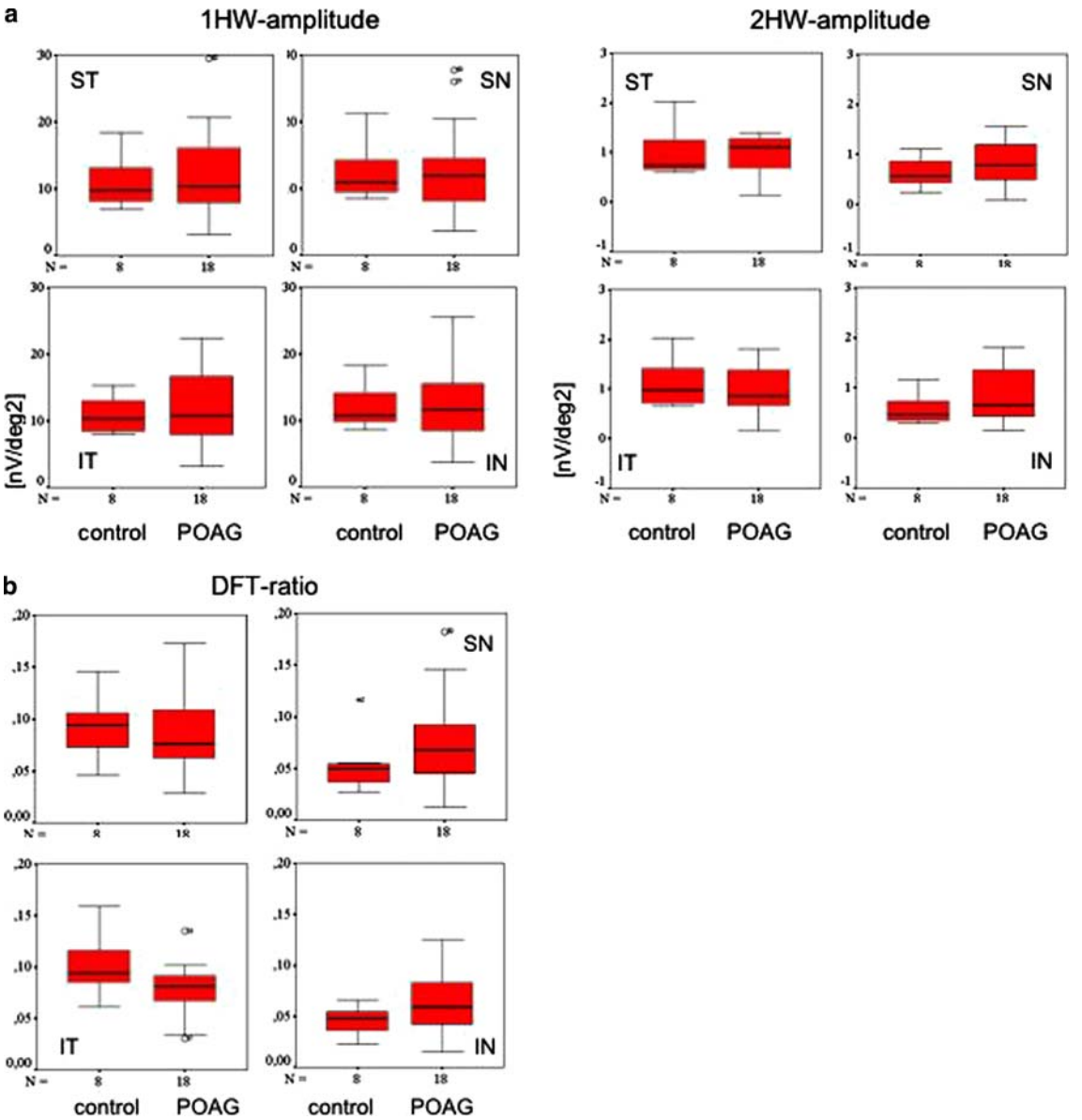

Fig. 3 Box plots of the responses averaged in quadrants. For each quadrant, the control group is plotted to the left and the POAG group is plotted to the right. (**a**) From left to right: the amplitudes of the 1HW and the amplitudes of the 2HW; (**b**) box plot of the DFT-ratio

significant difference between the control- and the POAG-group. In all response averages tested, this held true for the amplitudes and phases of the 1HW and the 2HW as well as for their amplitude ratio (DFT-ratio).

The DFT-ratio has been suggested to be the most sensitive parameter to distinguish a group of glaucoma patients from control subjects. However, in our study the DFT-ratio differed little between the groups. When we use our overall DFT-ratio to calculate the sample size needed to detect a significant group difference ($P < 0.05$, power: 0.8) between glaucoma patients and the control group, we would need to record from 640 patients and 284 control subjects. If so many need to be recorded to obtain a

Table 2 The corresponding *P*-values for the effects of location (Huynth-Feldt), the between subject effect and the influence of age for the responses averaged in quadrants and for the responses averaged over the 4 neighbouring hexagons in each quadrant

		Quadrants (*P*-value)	4 Areas (*P*-value)
Ampl 1HW	Location	0.133	0.055
	Subjects	0.542	0.524
	Age	0.121	0.132
Ampl 2HW	Location	0.741	0.415
	Subjects	0.512	0.471
	Age	0.112	0.538
Phase 1HW	Location	0.166	0.194
	Subjects	0.213	0.071
	Age	0.290	0.251
Phase 2HW	Location	0.355	0.878
	Subjects	0.464	0.280
	Age	0.432	0.281
DFT-ratio	Location	0.411	0.274
	Subjects	0.980	0.554
	Age	0.776	0.208

statistically significant group difference, this does not constitute a sensitive clinical test to detect glaucoma. However, from Fig. 3 it seems that looking at the DFT ratio of a smaller area might be more appropriate. When averages in quadrants and in the smaller areas of 4 neighbouring fields were looked at, the DFT ratio of the inferior temporal quadrant had the highest power (0.5). Using this parameter to find a significant group difference ($P < 0.05$, power: 0.8) between glaucoma patients and the control group, we would need to record from 31 patients and 41 control subjects. Thus, even using this parameter, the 30 Hz flicker mfERG under these conditions does not appear to be a sensitive enough clinical test to detect glaucoma, especially in an individual patient.

In glaucoma patients some authors found the DFT-ratio to be lower within the perimetric defect than outside the defect [14–16]. Our results were not in agreement with these results as we found no statistically significant correlation between the visual field values and the mfERG-parameters.

Our study differed from the previous studies in the following: In our study we used a 30 Hz flicker stimulation where all stimulation segments flicker at a frequency around 30 Hz (29.14–30.89 Hz). A 100 ms flicker phase is followed by a 100 ms dark phase. The focal responses are extracted by a Fourier transform analysis. In contrast hereto, in a previous study [14] the 30 Hz stimulation was trigged by an m-sequence step, resulting in a different way to extract the focal responses. However, when these different stimulation techniques were compared in healthy eyes, responses differed only in that the method used in our study was reported to have a better signal-to-noise ratio of about 2-fold [25].

According to the Standards of the International Society for Clinical Electrophysiology of Vision, the 30 Hz-flicker ERG is used to evaluate outer retinal function [19]. As the critical fusion frequency of rods under photopic conditions is below 15 Hz, the 30 Hz-flicker response is generated primarily by the cones [26]. The results of the 30 Hz-flicker ERG may also depend on which specific type of stimulation was used. For instance the contribution of bipolar cells has been suggested to be enhanced by a sinusoidally modulated stimulus [17], as was used in our study and also in the study mentioned below [18].

Recently, several studies using pharmacological agents to block post-photoreceptoral responses in the monkey have described that, in addition to the contribution from cones and bipolar cells [17], more proximal neurons are supposed to reflect the flicker ERG responses at higher frequencies [18]. For instance, blocking the activity of ganglion and amacrine cells resulted in a decline of the second harmonic wave amplitude and phase at a stimulation of 8 Hz, becoming very small at 30 Hz [18]. When the activity of bipolar cells was then blocked in addition, the fundamental base wave amplitude was found to decrease with increasing stimulus frequency, particularly between 8 Hz and 60 Hz. The authors found that not only is the second harmonic much smaller than the fundamental, but they also concluded that, in the flicker ERG inner retinal contributions to the first fundamental are present, but relatively small compared to the bipolar cell contribution. In the second harmonic wave the outer and inner retinal contributions are more equal between 2 Hz and 16 Hz stimulation. These findings were also confirmed in 2 human subjects [18]. Thus, while the human 30 Hz flicker ERG

contains contribution from inner retinal neurons [18], these contributions are small. This may explain why, in a clinical setting, with a stimulus rate of 30 Hz the flicker ERG is not very sensitive to early glaucomatous damage, where ganglion cells have been reported to be affected first [2].

In conclusion, the glaucoma group did not differ significantly from the control group either in their DFT ratio, amplitudes or phases of the 1HW and the 2HW. Within the glaucoma group no significant correlations were observed between the mean defect of the visual field and the mfERG parameters. Thus, under the stimulus conditions applied here (luminance, contrast), the 30 Hz-LED-flicker mfERG with cyclic stimulation does not appear sensitive enough to separate glaucoma patients from normal in a clinical setting.

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