Title page

Title: Visual fields correlate better than visual acuity to severity of diabetic retinopathy

Short title: B Bengtsson et al.: Visual fields and visual acuity in diabetic retinopathy

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Abstract
Purpose: To compare outcome of perimetric and visual acuity tests in patients with diabetic retinopathy.
Methods: Fifty-nine diabetic patients with different degrees of retinopathy were subjected to stereo fundus photography according to the Early Treatment Diabetic Retinopathy Study (ETDRS), and fluorescein angiography. Conventional White-White-Perimetry (WWP) and Short-Wavelength-Automated-Perimetry (SWAP) were performed and analysed with reference to normal values. Visual acuity (VA) was measured with ETDRS charts.
Results: Regression analysis revealed that VA was significantly associated with increasing severity of retinopathy according to the ETDRS scale when VA was estimated by counting LogMar Scores, but not by the conventional reading of the smallest line that could be seen,. VA decreased by 0.02 LogMar/ETDRS step (p=0.03). Degree of visual field loss was significantly associated with increasing severity of retinopathy according to the ETDRS scale, perimetric sensitivity decreasing by 0.44 dB/ETDRS step (p=0.0001) using WWP, and by -0.40 dB/ETDRS step (p=0.04) with SWAP. Area of the foveal avascular zone (FAZ) and adjacent perifoveal intercapillary areas (PIAs) also affected the central visual field as obtained both by WWP, –2.6 dB/ mm^2 (p=0.03), and by SWAP, –7.9dB/ mm^2 (p=0.002), but did not affect VA.
The regression model fit for peripheral retinopathy according to the ETDRS scale was better using WWP than SWAP or VA, while SWAP testing was superior to both WWP and VA when measuring effects caused by enlarged FAZ and PIAs.
Conclusion: Perimetry can provide more useful information than VA on functional loss in diabetic retinopathy, particularly when the perifoveal capillary network is damaged.

Key words:
diabetic retinopathy, foveal avascular zone, perimetry, visual acuity, visual fields

Abbrevations:

dB	decibel
ETDRS	Early Treatment Diabetic Retinopathy Study
FAZ	foveal avascular zone
Fig.	Figure
HFA	Humphrey Field Analyzer
LOCS	Lens Opacities Classification System
LogMar	logarithm of minimum angle of resolution
MD	Mean Deviation
PIA	perifoveal intercapillary area
r^2	coefficient of determination
SITA	Swedish Interactive Threshold Algorithms
SWAP	Short-Wavelength-Automated-Perimetry
VA	Visual acuity
WWP	White-on-White Perimetry

Introduction

Diabetic retinopathy is a major cause of acquired blindness before 65 years of age in the industrialized countries in the western world, but is also a rapidly increasing problem in urban areas in the developing countries [1]. Once sight-threatening vascular changes have developed, laser therapy has been shown to substantially reduce the risk for visual loss [2], but prevention or delayed progression of vascular abnormalities necessitates regulation of the hyperglycemic and related metabolic disturbances by systemic drug therapy [3]. The effects of drug therapy have been and are still monitored using photographic assessment of morphologic vascular changes in the retina according to a gold standard using severity scales based on findings from seven stereo fundus photographs of specified retinal fields. The scale presented by the ETDRS group is probably one of the most widely accepted and used scales [4], but it would be of great value to be able to assess the course of diabetic retinopathy not only by morphology but also by monitoring visual function.

Conventional WWP has been reported to enable identification of retinal changes caused by diabetes at early stages [5–6], and selective loss of short wavelength sensitivity has been reported in diabetic patients with no or minimal retinopathy [7–8]. Blue-on-yellow, or SWAP, has been suggested to be more sensitive to early retinal changes than WWP. A number of studies have compared SWAP and WWP in patients with diabetes [9–13], but the results are not conclusive regarding the relative usefulness of these two tests. Few studies have assessed to what extent perimetry can document functional loss due to diabetes-induced damage of the perifoveal capillary network [10].

In the present study, we have taken interest in exploring visual field defects in diabetic patients and comparing WWP and SWAP test modalities. The Statpac MD and Pattern Deviation probability map concept was used to analyse all perimetric test results [14]. To that end, we collected a new normal database and created new normal limits when needed in the same way as in the Statpac program.

The primary aim of this study was to assess visual field defects using both conventional WWP and SWAP in patients with different degrees of diabetic retinopathy according to the ETDRS severity scale. The secondary aim was to correlate visual field data to vascular occlusion in the foveal region, i.e. the area of the FAZ and the most adjacent PIAs as visualized by fluorescein angiography.

Subjects and Methods

Subjects

Patients with different degrees of diabetic retinopathy, regularly attending the outpatient clinic at the Department of Ophthalmology, Malmö University Hospital, gave their informed consent to participate in the present study, which was approved by the Ethics Committee of Lund/Malmö. Inclusion criteria were: age less than 70 years, no ocular disease that could impact visual function apart from diabetic retinopathy and minimal to mild cataract, and no previous laser treatment of the examined eye. One eye of each patient was included. If both eyes were eligible and had different visual acuity, the eye with best visual acuity was selected. Data on age at diagnosis, and duration of diabetes were collected.

Characterization of vascular changes and cataract

Fundus photography and grading of retinopathy

After dilatation of the pupil, stereo fundus photographs of seven 35° standard fields of the retina [4] were taken using a Topcon TRC 50 IX retinal camera and colour slide film (Kodachrome 64). Grading of retinopathy was performed in a masked fashion using the 11 steps of the ETDRS severity scale [4]. Macular edema was defined as any thickening of the retina within the vessel arcades.

Fluorescein angiography

Fluorescein (25%) angiography was performed after dilatation of the pupil. Digital images were taken using a Topcon TRC 50 IX retinal camera in one 35° field, centred on the fovea, and processed in the Topcon Image Net 2000 system. The borders of the FAZ and each PIA adjacent to the avascular zone were marked as described by Sleightholm et al. [15] (Fig. 1), and the areas were calculated using the commercially available Topcon Image Net 2000 system software. FAZ borders were defined on two different occasions one week apart. The concordance between the two independent measurements was high; the correlation coefficient was 0.99 when including all subjects with measurable FAZ. After excluding one outlier, having a very large FAZ of 3.9 mm^2, the correlation coefficient was 0.93.

Cataract

Presence of lens opacities was graded using a slit lamp microscope and the LOCS II [16].

Characterisation of visual function

Visual acuity

The ETDRS charts [17] were used when measuring VA. Best corrected visual acuity was estimated in two ways: 1. by the smallest line on the chart where the individual could read all letters 2. by counting LogMar scores [18], i.e. a threshold estimate of VA.

Visual field tests

All visual fields were tested using the HFA 750 (Carl Zeiss Meditec, Dublin, California, USA). To minimise perimetric learning effects, a training session was performed for both WWP and SWAP at a first visit. At a second visit, the patients underwent four different perimetric examinations, two with SWAP and two with WWP. For each test modality we obtained one 24-2 field including 54 test point locations within the central 24° of the visual field, and one high resolution 10-2 field with 68 test points covering the central 10°. All subjects were tested in the same order: 24-2 SITA SWAP [19], 10-2 Full Threshold SWAP, SITA Standard 24-2 WWP, and a 10-2 SITA Standard WWP. In general, durations of the different tests were 3 minutes for SITA SWAP 24-2, 12 minutes for Full Threshold SWAP, 4 to 5 minutes for both 10-2 and 24-2 SITA Standard WWP. Despite the short test times for most perimetric programs, all patients were required to rest between the visual field tests to avoid fatigue effects. The Statpac program implemented in the HFA [20] was used to interpret the results of the WWP, while a preliminary Statpac was used to interpret 24-2 SITA SWAP [21]. No criteria were applied on the reliability parameters; frequencies of fixation losses, false negative and false positive answers. Fixation Loss monitoring using the blind spot method does not perform well in SWAP, since in SWAP a Goldmann stimulus size V is used. A large percentage of subjects report seeing the large bright stimulus when it is exposed in the blind spot, even when fixation is perfect when checked on the screen monitor. High frequencies of false answers can seriously affect test results, but were not used as an exclusion criterion in this study. The purpose was to test applicability of perimetry in an

ordinary clinical setting of patients at different stages of diabetic retinopathy, and not in elite observers.

No Statpac limits were available for the 10-2 Full Threshold SWAP test. To be able to analyse these visual field tests using the same parameters as those applied for the other tests, we collected a normal database including 180 eyes of 90 healthy subjects and calculated a new Statpac for 10-2 SWAP. The mean age of these healthy subjects was 45 years (range 20 to 79). They had no or very limited experience of perimetry. Therefore, all subjects went through a training session for both WWP and SWAP prior to inclusion. The 10-2 SWAP normal database was then processed in a way almost identical to that of the original Statpac for WWP [14] (Fig. 2). Thus, MD values and Pattern Deviation probabilities maps, both included in the Statpac interpretation tool, were made available also for the 10-2 Full Threshold SWAP.

Statistical methods

Visual function and retinopathy according to the ETDRS scale

The 24-2 pattern, examining a larger area, was used when correlating degree of retinopathy according to the ETDRS scale [4] to visual field loss. The 10-2 pattern, testing inside the central 10° of the visual field, was used when comparing the area of FAZ and PIA to visual function.

The correlations between WWP or SWAP and the eleven steps of the ETDRS retinopathy scale were analysed by linear regression. Two visual field parameters were included in the analyses, MD values and number of significantly depressed test points in the Pattern Deviation Probability Maps at the $p<1\%$ level.

Effects of retinopathy on VA was also analysed by linear regression

Visual function and FAZ + PIAs

Effects of the size of FAZ and PIAs on the central and paracentral visual field were analysed using multivariate linear regression models. To avoid dilution of the effects caused by more peripheral retinal damage, new MD values (6°MD) were calculated based on the 16 test points inside the central 6°. The 10° field including 68 test points covers approximately 6.25 mm^2 on the retina, while the 6° field covers approximately 2.25 mm^2. The maximum FAZ area among our patients was 1.47 mm^2 after exclusion of one extreme outlier with a FAZ area of 3.9 mm^2. The number of significantly depressed points at the $p<1\%$ level inside the same central 6°area was compared to FAZ and PIAs, and also to the number of PIAs.

Presence/absence (20/38) of macular edema was also included to avoid confounding effects. Association between FAZ + PIAs and VA was estimated by linear regression

Results

Out of the 63 patients included, 59 completed all examinations. Thus, most analyses are based on 59 patients. Twenty-three patients on insulin treatment who were younger than 30 years of age at diabetes diagnosis were considered as having type 1 diabetes, and the remaining 36 as having type 2 diabetes. Mean age at time for this study was 50.6 years, ranging from 20 to 69, age at diabetes diagnosis was 35.0 years, ranging from 2 to 62, and diabetes duration was 15.8 years ranging from 0 to57 years.

Visual function in patients with different degrees of diabetic retinopathy according to the ETDRS severity scale

All patients performed perimetry well according to the reliability indices: false positive and false negative responses. The frequency of false positive answers ranged from 0 to 28%, the median was 7%, and the mode value was 0%. Only two subjects had frequencies of false positive answers larger than 15%. Frequencies of false negative response ranged from 0 to 16%, with a median and mode value of 0%.

Both WWP and SWAP correlated significantly to the level of diabetic retinopathy when considering total loss as expressed by MD values, p=0.0001 and p=0.04 respectively (Fig. 3). The regression model fit was better for WWP, with an r^2 of 0.23, than for SWAP, with an r^2 of 0.07. As expected, MD values were worse (more negative) in eyes with more advanced retinopathy.

Localised visual field loss, as measured by the number of significantly depressed points at the p<1% level in Pattern Deviation Maps, increased with 0.67points/ETDRS step (p=0.002) with WWP. With SWAP the increase was 0.41 abnormal points/ETDRS step, but this was not significant (p=0.26).

There was no significant association between VA, as estimated by the conventional smallest line that could be read, and diabetic retinopathy as graded by the ETDRS scale (p=0.17). We found a significant correlation, however, when estimating VA by counting LogMar scores. VA decreased with 0.02 LogMar/ETDRS step (p=0.03), but the r^2 was only 0.08.

Influence of cataract

Most subjects had no or mild cataract. Nuclear cataract was absent (N0) in 42 eyes, mild (N1) in 16. Cortical cataract was absent (C0) in 43 eyes, minimal (C1) in 13 and mild (C2) in 13 eyes. Posterior subcapsular cataract was absent (PS0) in 48 eyes, minimal (PS1) in 9 and mild (PS2) in 1 eye. The effect of cataract on the visual field was negligible or small and when adding the individual sums of the LOCS II grading as an explanatory variable (p=0.95) to the regression model analysing the effect of retinopathy on the WWP visual field. Neither were effects of cataract significant on the SWAP fields (p=0.14).

Visual function vs. FAZ and PIAs

Forty-six of the 59 subjects who underwent perimetry had high quality angiograms enabling accurate outlining of FAZ and PIAs and subsequent measurements of the areas. When estimating effects of size of FAZ on visual function, one outlier with a FAZ area of 3.9 mm^2 was excluded. The FAZ area for the other subjects ranged from 0.22 to 1.47 mm^2. The central 10-2 visual field of this outlier was much more damaged than those of the other subjects: WWP MD 10-2 was –9.3 dB (mean MD in the group was -1.2 dB) and the SWAP MD 10-2 was –14.8 dB (group mean was –2.67 dB). The number of significantly depressed points in the pattern deviation maps was also much higher than in the rest of the group. Inclusion of this outlier would yield a number of highly significant results and would improve the p-values of our analyses. As regression analysis is known to be very sensitive to outliers, this person was excluded from analyses. Thus, 45 subjects were included in the FAZ and PIA vs. degree of retinopathy, visual field and VA analyses.

There was poor correlation between the FAZ area alone and degree of retinopathy (p=0.38). However, when PIAs were included there was very clear correlation (p=0.0007). The number of PIAs represents a measure of the branching of the retinal perifoveal intercapillary network, the fewer the number, the more severe the damage. Accordingly, the number of zones was inversely correlated to the degree of retinopathy (p=0.03).

The size of FAZ alone was not enough to explain the 6°MD, but adding the size of PIAs to FAZ and also including number of PIAs in a multivariate regression analysis, the regression

models improved meaningfully as estimated by r^2: from 0.01 to 0.22 with WWP, and 0.03 to 0.35 with SWAP. Thus, larger FAZ and PIAs reduced perimetric threshold sensitivity, while at the same time increased number of PIAs improved threshold sensitivity.

In WWP the 6°MD decreased significantly (p=0.03) with 2.6 dB per mm^2 increase of FAZ and PIAs. More pronounced effects and higher significances were seen in SWAP in which the 6°MD decreased 7.9 dB per mm^2 increase of FAZ and PIAs (p=0.002). In SWAP the number of depressed test points increased significantly (p=0.03) with 4.4 points per mm^2 increase of FAZ and PIA, whereas no significant increase of such points were seen in WWP (p=0.48). Presence of macular edema did not affect the central 6° field significantly in SWAP (p=0.11) when including size of FAZ and PIAS in the same regression model.

Regression analyses did not reveal any significant correlation between the size of FAZ or the size of PIAs and FAZ together on one hand and VA on the other, neither when estimating VA by smallest line that could be read (p=0.23), nor when counting LogMar scores (p=0.08).

Discussion

In this study comparing VA and perimetric tests for functional loss in diabetic retinopathy, we found that the regression model fit for peripheral retinopathy according to the ETDRS scale was better using WWP than SWAP or VA, while SWAP testing was superior to both WWP and VA when measuring effects caused by enlarged FAZ and PIAs.

SWAP has been suggested as a useful tool for defining visual function loss in diabetic patients with early ischemic damage of the macula [10] or Clinically Significant Macular Oedema [9]. Decreased blue-on-yellow sensitivity has even been demonstrated in diabetic children without clinically detectable retinopathy [12]. Our results suggest that WWP might be better than SWAP in separating groups with different levels of retinopathy, while central SWAP appears superior to WWP in identifying more localised field loss caused by macular damage.

Since SWAP is considerably more affected by cataract than WWP, interpretation of SWAP fields using raw threshold sensitivity values, age-corrected threshold values or global indices such as mean sensitivity or MD could be misleading. The Pattern Deviation concept aims at eliminating effects of cataract on the visual field [22–23]. To our knowledge this study is the first to compare SWAP and WWP using empirically derived Probability Maps for SWAP 10-2 in diabetic patients. It might be very important to apply this concept when interpreting test results of diabetic patients, particularly as they tend to develop cataract earlier than healthy subjects [24]. Thus previous comparisons between WWP and SWAP in patients with diabetes could have been affected by cataract, even when age-matched control groups were included.

It was interesting to notice the difference between the two ways of estimating VA. The threshold approach [18] correlated better with severity of diabetic retinopathy than the conventional "read the smallest line that could be seen" method. This indicates that LogMar scores are more sensitive and should be preferred when assessing visual function with VA.

In non-diabetic subjects, the extension of FAZ has been reported to be between 0.2–0.4mm^2 [6, 10, 25–27]. FAZ is enlarged in diabetic patients with retinopathy [26], particularly in those with reduced visual acuity [28]. We found no significant relation between VA and FAZ, and no clear correlation between FAZ area and retinopathy level as graded by the ETDRS scale, but when adding the size of PIAs to the FAZ area there was a significant correlation in agreement with the result obtained by Arend et al. [29], indicating damage to the macular capillary network along the course of diabetic retinopathy. Such damage correlated better

with SWAP than with WWP or VA. SWAP has also been reported to be more sensitive for macular edema than WWP [9]. In our analysis the presence or absence of macular edema did not influence the correlation between the FAZ-PIAs and SWAP sensitivities, however. Thus, including presence of macular edema in the same regression model, did nor change the slope or p-value for FAZ and PIAs.

By including the outlier with the FAZ extending to the periphery of the macula, we could have demonstrated highly significant effects of FAZ both on general and localised field loss ($p<0.0001$ in both cases and with both methods). We believe, however, that an excessive impact from one single outlier should be interpreted with great caution, and therefore we excluded this subject from the analyses including FAZ and PIAs.

Some of our results are in conflict with those reported by Henricsson & Heijl 1994 [30]. They found no significant influence of diabetic retinopathy on WWP in eyes with mild retinopathy, but clear evidence at more advanced stages (ETDRS 43 or higher). In our sample 24% of the subjects with mild to moderate retinopathy, defined as ETDRS levels less than 43, had significantly depressed fields as measured by MD values, and 46% of our patients had more than twice as many abnormal points as expected in a normal eye. There is no obvious explanation for the different results of the two studies, apart from improvements in diagnostic techniques.

In summary, visual function as measured by perimetry, correlated with the degree of diabetic retinopathy according to the ETDRS scale as well as with the extension of the foveal avascular zone and adjacent perifoveal intercapillary areas. Conventional WWP was at least as sensitive as short wavelength automated perimetry for the various ETDRS steps, but SWAP was more sensitive to abnormalities in the foveal capillary network. Angiographically visualised FAZ and PIAs represent measures of central vascular damage, but since they did not correlate well with visual acuity impairment, perimetry seemed more useful when monitoring visual function as a measure of the extension of the FAZ and PIAs. Thus, our results suggest that perimetry match and can provide additional useful information to conventional photographic documentation when monitoring patients with diabetic retinopathy. However, longitudinal studies are needed to prove definite value of perimetry in the follow-up of patients with diabetic retinopathy.

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Conflict of interest

Our department has a contract including perimetric development with Zeiss-Meditec, the manufacturer of the perimetric instruments used in this study, but has received no support for this specific project.

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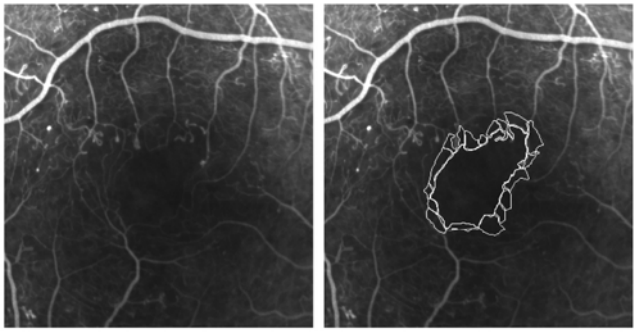
Legends

Figure 1. FAZ (marked zone in the middle) and adjacent PIA (all marked zones surrounding the central in the middle) in a thirty-year-old patient with type 1 diabetes (a). Corresponding visual field defects on WWP (b) and SWAP (c). Grey-scale representations are based on differential light sensitivity values expressed in dB. Probability maps show the statistical significance of test point locations with sub-normal sensitivity values after eliminating effects of cataract.

Figure 2. Profile of the hill of vision along the horizontal meridian for a right eye. WWP age-corrected normal values (a) WWP depression needed to the reach p<1% limit (b). SWAP age-corrected normal values (c) lower SWAP sensitivities needed to the reach p<1% limit (d).

Fig 3. Using WWP (a), MD decreased with 0.44 dB for each ETDRS step (p=0.0001). With SWAP (b) the slope was 0.40 dB/ETDRS step (p=0.04).

a



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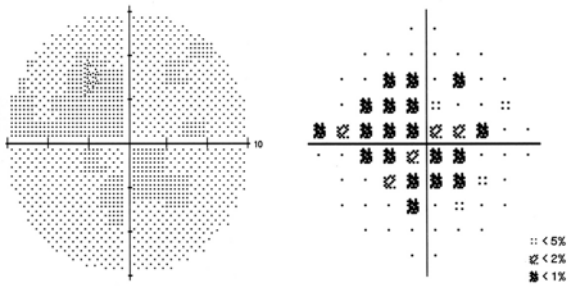
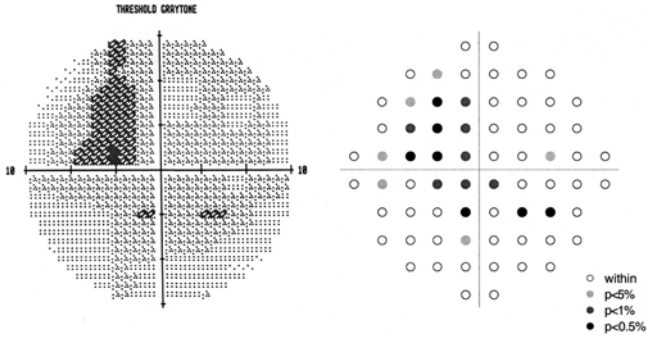


WWP

c



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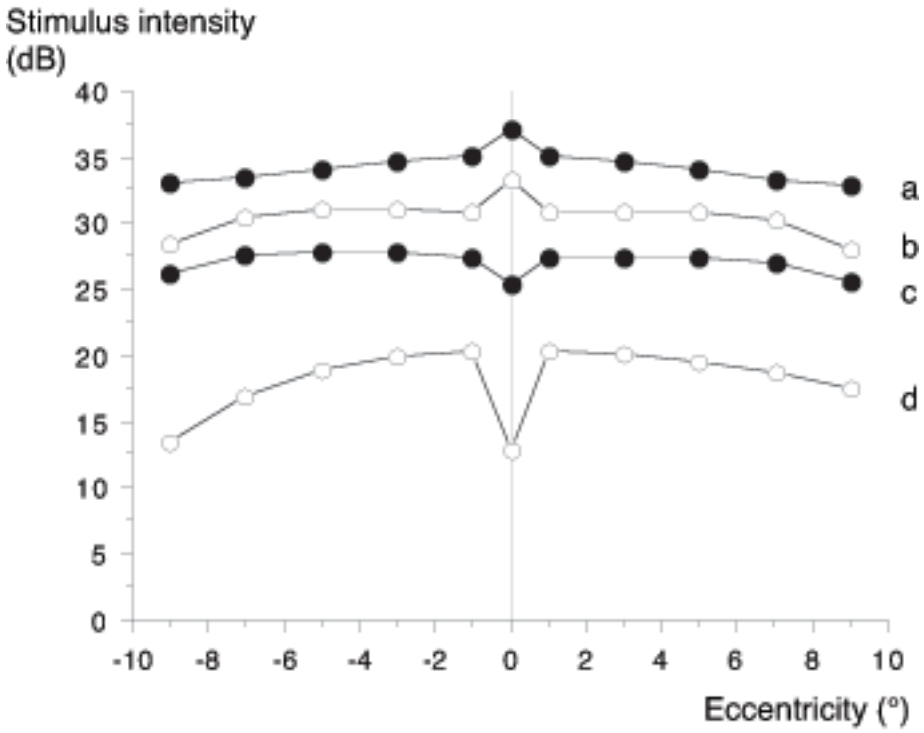
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(dB)
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35
30
25
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15
10
5
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-6
-4
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8
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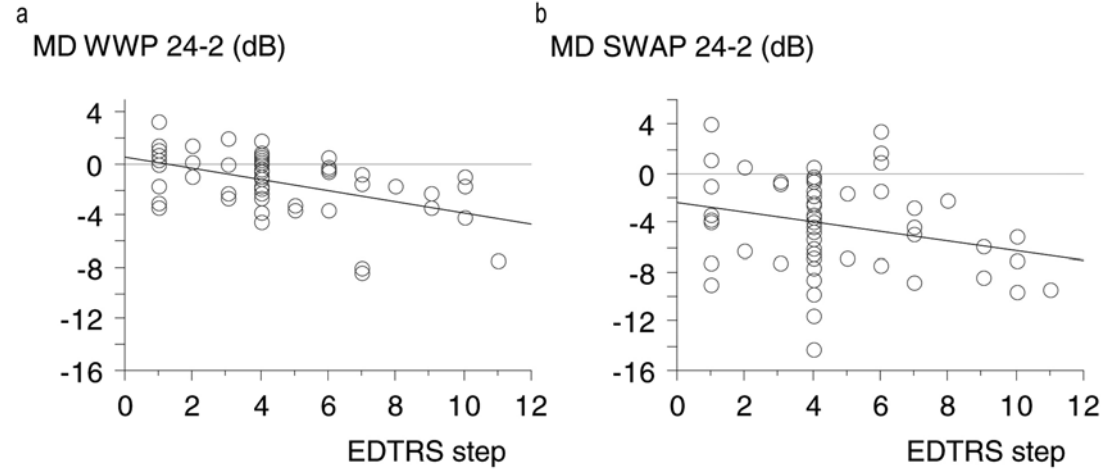
Eccentricity (°)
a
b
c
d


a
MD WWP 24-2 (dB)
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EDTRS step
b
MD SWAP 24-2 (dB)
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