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The Components of Variability Associated with Perimetry Including a New Term, Called Medium-Term Fluctuation

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Für meine Eltern mit herzlichem Dank

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1. Introduction

The identification of visual field loss at the earliest stage is essential for the optimum detection of open angle glaucoma (OAG) whilst the delineation of progressive field loss at the earliest opportunity is essential for the successful management of the disease.

The outcome of any given visual field examination is limited by the inherent variation, or fluctuation, in the threshold estimate [1-18]. The variability comprises several components. The short-term fluctuation (SF) describes the variance in the threshold estimate at a given stimulus location occurring within a single examination, i.e. over a period of seconds to minutes. It essentially denotes the measurement error associated with the determination of threshold [2] and is usually represented in terms of a summary measure of the fluctuation occurring across all of a given number of stimulus locations. The long-term fluctuation (LF) describes the variance of the threshold estimate occurring between examinations, i.e. over an interval of days to years. The LF is additional to that of the SF and comprises the homogenous component, LF(Ho), which is the variance affecting all stimulus locations equally, and the heterogeneous component LF(He) which is the variance that differs between the various stimulus locations [7-8,16]. The two LF components each represent summary measures of the fluctuation occurring across all the specified locations.

The number of stimulus locations per visual field examination represents a compromise between the optimum detection of a given area of field loss and a realistic examination duration. Automated static threshold perimetry generally utilizes between 56 and 76 stimulus locations within 24º-27º eccentricity from fixation per examination. The stimuli are usually based upon a square grid with an inter-stimulus separation of 6º. Such a stimulus grid enables the detection of a focal defect of approximately 7º in diameter – i.e. a scotoma the size of the blind spot – with a probability of 95% [18].

Enhanced spatial resolution in perimetry, and therefore the detection of a smaller area of field loss, can be achieved by the application of a high-

resolution grid at a 'region of interest' (ROI) [19-25]. By concentrating stimuli at those locations exhibiting a high index of suspicion of glaucomatous damage or of progressive glaucomatous field loss, superfluous stimulus presentations in regions with minor diagnostic relevance can be avoided. Such a technique yields a higher probability of detection of early glaucomatous field loss than the conventional grid based upon an inter-stimulus separation of 6º [21]. However, the procedure can result in an unnecessarily lengthy examination with the associated problem of patient fatigue which, in turn, leads to an artifactual lowering of the differential light sensitivity at locations exhibiting intermediate values of sensitivity [26-32].

The advent of statistically- and computationally-intensive perimetric threshold algorithms such as the Swedish Interactive Threshold Algorithms (SITA) [33-40] and Tendency Oriented Perimetry (TOP) [41-44] have resulted in a marked reduction in the duration of the visual field examination. The SITA algorithms have largely replaced the first generation algorithms such as Full Threshold and FASTPAC. The 'saving' in the examination duration relative to the older algorithms provides an opportunity, at the same patient visit, either for an identical confirmatory examination to verify the apparent presence of abnormality or the apparent progression of existing abnormality; or for a supplementary examination to enhance the spatial resolution of the stimulus grid used for the detection of abnormality. However, the extent of the variation in the threshold estimate at a given stimulus location between two such consecutive visual field examinations on the same eye separated by an interval of minutes to several hours, i.e. the medium-term fluctuation, MF, is unknown. Without such knowledge, the results arising from the use of a confirmatory examination cannot be interpreted with assurance and confidence.

The overall aim of the study, therefore, was to determine, in stable OAG, the MF between two consecutive visual field examinations undertaken after a suitable rest period on the same eye thereby facilitating the separation of abnormality and/or of progressive abnormality from the fluctuation in the threshold estimate. The specific aims were threefold: Firstly, to determine the

contribution of the MF to the total variation associated with the threshold estimate. Secondly, to determine the distribution of the MF and the corresponding reference intervals. Thirdly, to determine the relationship between the magnitude of the MF and the summary visual field indices.

2. Methods

The cohort initially comprised 41 eyes of 41 consecutively presenting volunteer patients with OAG who met the inclusion criteria for the study (17 male, 24 female). The mean age was 50 years (SD 15 years; range 13 to 73 years). All patients manifested an optic nerve head characteristic of OAG (including an increase in cup size, increase in cup to disc ratio, disc asymmetry, changes in the lamina cribrosa, loss of neuroretinal rim, pallor, evidence of peripapillary atrophy, vessel changes or disc margin haemorrhage) [45]. The exclusion criteria comprised a visual acuity of 20/40 or worse in each eye; a distance refractive error greater than ±8.00DS and greater than -3.00DC; clinically significant cataract determined through dilated pupils by slit lamp examination; gonioscopic evidence of anterior chamber abnormality or angle closure; optic nerve disorder not attributable to glaucoma; systemic medication known to affect the visual field; history, or family history, of diabetes mellitus; history of CNS disorder; previous intraocular surgery; and ocular trauma or inflammation.

All patients manifested well-controlled intraocular pressures (group mean 16.5 mmHg; SD 3.6 mmHg). Fourteen patients were controlled on a single topical agent (either a selective or non-selective β blocker, a topical carbonic anhydrase inhibitor, a prostaglandin or an alpha agonist); 18 patients required more than one topical agent for intraocular pressure control. Nine patients did not receive any topical agent during the course of the study. No patients were on systemic carbonic anhydrase inhibitors. Three patients had undergone previous trabeculectomy, one of whom was not receiving any topical agents at the time of the study. All patients were experienced in the requirements of automated threshold static perimetry.

The MF was calculated in the context of one method of high-resolution perimetry, namely Fundus-oriented perimetry (FOP) [19-25] using the Tübingen Computer Campimeter (TCC). Perimetry was undertaken in one designated eye of each patient. The designated eye from each patient was selected so as to

bias the severity of the field defect within the sample towards mild loss but, at the same time, provide a continuum of severity across the sample.

The TCC incorporates a calibrated high-resolution (75 dpi, 1024 × 768 Pixels) video display unit (BARCO Calibrator, The Barco Company, Kippenheim, Germany) instead of a cupola [22-25, 46, 47]. The 20 inch monitor covers a visual field of approximately 35° horizontally and 24° vertically at a viewing distance of 30 cm. The background luminance is 10 cdm^{-2}. The stimulus size is Goldmann III which subtends 0.431°. The maximum stimulus luminance is 68cdm^{-2} and the minimum luminance is 0.19 cdm^{-2}. The fixation target is diamond-shaped and consists of four red circles with a luminance of 12 cdm^{-2}, each subtending 15 minutes of arc and each located at an eccentricity of 1°. Fixation is monitored by an infrared-videographic device which records objective pupil data (pupil diameter and position/fixation coordinates); and by the number of false-responses to the presentation of a 5dB threshold related suprathreshold stimulus at the fovea. The patient was re-aligned, where necessary, by the examiner during the examination.

FOP generates an individual “evidence based” grid for each patient which is tailored to, and centred upon, a ROI corresponding to suspicious or manifest changes in the optic nerve head or fundus [19-25]. The ROI for each eye is defined from stereo-observation of the fundus and is spatially located with the aid of fundus photographs covering the area from the macula out to 50° eccentricity. The spatial density of the conventional 6º square stimulus grid out to 30º eccentricity, incorporating 73 stimulus locations, is enhanced by 64 additional stimulus locations in the designated ROI. The additional stimulus locations are added to the ROI by an iterative algorithm that ensures a constant inter-stimulus separation in the ROI. Thus, a maximum of 137 possible locations can be examined. The total number of stimuli presented and the magnitude of the inter-stimulus separation is a function of the area(s) of the ROI(s). Nine identical reference locations within each grid permit evaluation of the between-session variability. One of the nine reference locations is situated at fixation, the remaining eight are situated along the oblique meridians, four at 12.7º

eccentricity and four at 29.7º eccentricity respectively. The total number of stimuli is presented over two sub-examinations. Each sub-examination contains stimuli randomly allocated from the conventional grid and from the grid corresponding to the ROI.

FOP uses a modified 4-2-1-1 dB staircase strategy with 4 reversals of threshold. Threshold is calculated by maximum-likelihood estimation using custom software.

The designated eye of each patient was examined at three visits with each visit consisting of the two sub-examinations. The two sub-examinations were undertaken on the same day after a rest period. The mean interval between the two sub-examinations at the first visit was 16.2 min (SD 12.3 min; range 1.8 to 62.2 min). The second and third visits were undertaken after intervals of 224 ± 80 days (mean ± SD) and 228 ± 62 days, respectively. The mean interval between the two sub-examinations at the second visit was 11.4 min (SD 12.8 min; range 3.5 to 80.3 min) and at the third visit 11.5min (SD 19.1 min; range 2.2 to 121.1 min). The visual fields for each patient at each sub-examination of each of the three visits exhibited stable fixation and ≤33% false responses to the false-positive and to the false-negative catch trials, respectively.

In 114 of the 123 sub-examinations (93%), each sub-examination comprised 73 stimulus locations. In 7 sub-examinations (4 patients), the number of stimulus locations within each sub-examination varied between 67 and 73 with the greatest difference for a given patient being 4 locations. In one patient, the number of stimulus locations in each sub-examination was 70.

The degree of field loss at the first of the three visits was classified based upon the system of Hodapp and colleagues [48]. This system describes the severity of field loss in terms of the Mean Deviation (MD) index and in terms of the number, severity and proximity to fixation of the Pattern Deviation (shape analysis) probability symbols. The classification was based upon the sensitivity derived at the stimulus locations contributing to the 6° grid across the two sub-examinations and was adjusted pro-rata between-patients for the minor

reductions in the number of stimulus locations from the established 76 upon which the classification system is based. The cohort comprised 19 eyes without field loss, 5 with minimal loss, 6 with early loss, 7 with moderate loss and 4 with severe loss. The unweighted MD of the visual field ranged from -1.72 dB to 8.03 dB; visual field abnormality being designated by a positive MD.

The optic nerve head was assessed over the duration of the study by a single experienced clinician (Ulrich Schiefer). The stability of the optic nerve head appearance was evaluated by stereo-observation and defined in terms of the absence of new or increased notching, new or increased saucerization, increased cup to disc area ratio, or new haemorrhage.

The stability of the visual field for each patient over the duration of the study was determined by a group of four independent raters and was based upon a consensus opinion of the pattern of the field loss and the magnitudes of the MD and of the Total and Local Loss Volumes. The latter two indices are based upon a volumetric comparison of the normal hill of vision with that of a single patient and represent the height and shape analysis, respectively. The Total Loss Volume (TLV) describes the difference between the envelope curve of the age-correlated normal hill of vision (or, more accurate, its 5% reference area) and that of the patient's hill of vision that was determined in the examination. The Local Loss Volume (LLV) is determined the same way as the TLV, but concentrates upon a region of interest (ROI) that can be chosen freely [49].

The research followed the tenets of the Declaration of Helsinki, informed consent was obtained from each subject after the nature and possible consequences had been explained and the study had approval from the Institutional Review Board of the University of Tübingen.

The magnitudes of the MF, SF and LF and their contribution to the total variation in the threshold estimate were firstly determined across all three visits using a multi-factorial analysis of variance (ANOVA) undertaken with the statistical software JMP (Version 4.0.2, SAS Institute Inc. Cary, NC.). The components of variation in the threshold estimate were calculated using the

formula of Flammer et al. [50] and Hutchings et al. [7; 16] which was additionally nested for the factor “patient”:

$$Y_{ijkm} = \mu + P_i + L_{ij} + V_{ik} + LV_{ijk} + M_{ikm} + E_{ijkm}$$

where,

Y_{ijkm} is the threshold estimate for patient i at test location j at visit k, sub-examination m; μ is the mean of the threshold estimate over all examinations; P_i is the patient effect; L_{ij} is the effect of location j in patient i; V_{ik} is the effect of visit k in patient i and gives rise to the LF(Ho); LV_{ijk} is the interaction of location j and visit k in patient i and gives rise to the LF(He); M_{ikm} is the effect of sub-examination m at visit k of patient i and produces the MF; E_{ijkm} is the experimental error term and has a standard deviation SF; i is patient i = 1, 2, 3,…, 41; j is the stimulus location, j = 1, 2, 3,…, 9; k is the number of visits, k = 1, 2, 3; and m is the number of the sub-examinations, m = 1, 2.

The ANOVA also examined the contribution both of Systematic and Individual influences to the variance associated with the threshold estimate. The Systematic influences comprised the eccentricity of each reference stimulus location and the position with respect to the superior, inferior, nasal or temporal quadrants. The Individual influences comprised patient-related effects, namely: age, gender, eye examined, visual acuity, extent of glaucomatous visual field loss, e.g. stimulus localization inside or outside a scotoma [51-53], and the cooperation, and motivation, of the patient. The Systematic effects of the stimulus location and the individual effects of each patient were summarized in order to fit a balanced model of analysis, thereby allowing the optimum ANOVA. All effects were nested within the patient effect P_i.

A further ANOVA was used to derive, for each patient, the magnitude in dB of the SF, MF, LF(Ho), LF(He), and systematic fluctuation across all three visits. In this second analysis, the results for each effect were considered in terms of the standard deviations of the conditional means when all other the factors were

fixed. Such an approach permitted comparison with the components of the LF derived by Hutchings et al [7] and Flammer et al [50]. All factors in the ANOVA were computed as maximum-likelihood estimates of the type:

$$\sqrt{\frac{\text{Sum of Squares of the factor}}{\text{Error Degrees of Freedom}}}$$

The resulting values for the LF(Ho), LF(He), MF and SF were each well described by a gamma distribution which was then used to estimate the respective median and the 90% reference intervals. An identical procedure was then undertaken to derive the median and the 90% reference intervals for the LF(Ho), LF(He), MF and SF, and systematic fluctuation between Visits One and Two and between Visits Two and Three, respectively.

Three additional ANOVAs were then calculated for each patient, in a similar manner, to derive the MF between the two sub-examinations at each of the three visits. A gamma distribution was again used to estimate the respective median and the 90% reference intervals for the MF at each visit.

3. Results

The contribution of each of the sums of squares from the ANOVA, encompassing all 41 patients and based upon all three visits, together with the corresponding SDs are shown in Table 1. The largest components of variation within- and between-examinations resulted from the Systematic influences and from the Individual influences of each patient. These two components contributed 90% of the total variation.

Component of variance	Percentage of sums of squares (%)	Root variance component (dB)
Individual influences	28.48	3.68
Systematic Influences	61.68	5.42
LF(Ho)	1.16	0.74
LF(He)	3.76	1.34
MF	1.10	0.72
SF	3.82	1.35

Table 1. The proportions of the sums of squares (%) and the accompanying maximum-likelihood estimate of the SD (dB) of each of the conditional means derived from the ANOVA for all 41 patients across all three visits.

The median and the 90% reference intervals (5^{th} and 95^{th} percentiles), estimated using the respective gamma distributions, for the distributions of the Systematic influences, the LF(Ho), the LF(He) the SF and the MF, based upon all three visits and derived from a separate ANOVA for each patient are shown in Table 2. The frequency distributions are shown in Figure 1. The corresponding values between Visits One and Two and between Visits Two and Three are also given in Table 2.

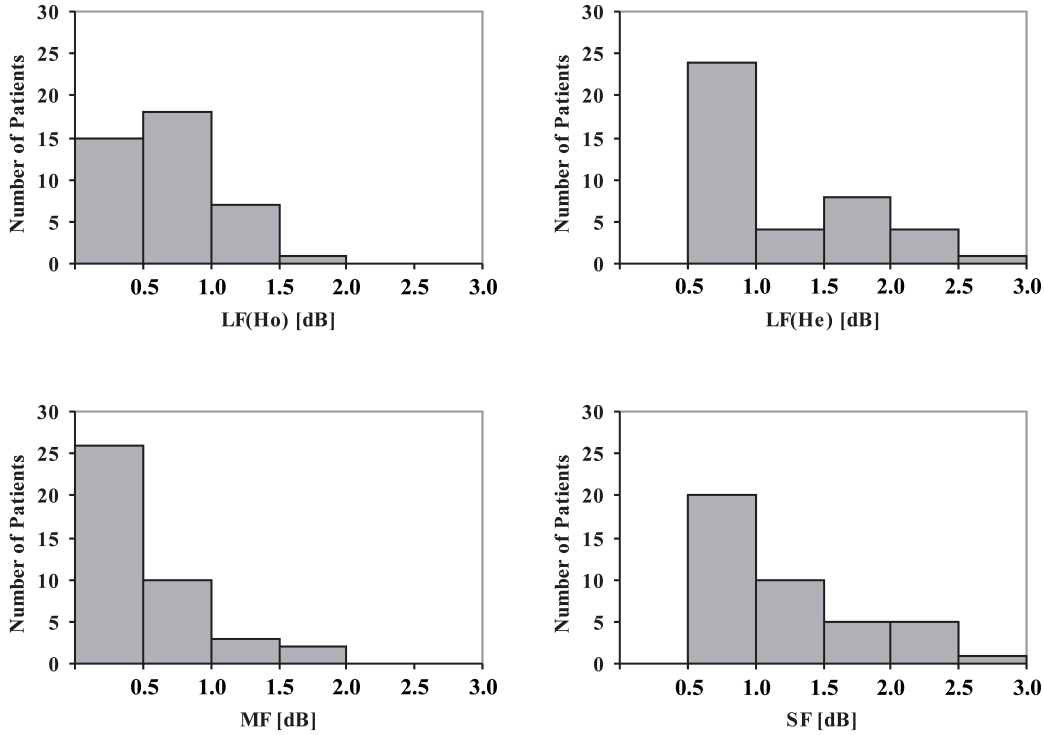

Figure 1. The frequency distribution of the LF(Ho) (top left), the LF(He) (top right), the MF (bottom left) and the SF (bottom right) derived from the separate ANOVAs for each of the 41 patients across all three visits.

Component of variance	Median (dB)	5th Percentile (dB)	95th Percentile (dB)
Systematic influences			
Visits One, Two and Three	**4.92**	3.18	7.68
Visits One and Two	**4.95**	3.11	7.76
Visits Two and Three	**5.17**	3.26	7.94
LF(Ho)			
Visits One, Two and Three	**0.57**	0.14	1.44
Visits One and Two	**0.39**	0.06	1.21
Visits Two and Three	**0.43**	0.03	1.59
LF(He)			
Visits One, Two and Three	**0.93**	0.49	2.20
Visits One and Two	**0.76**	0.37	1.86
Visits Two and Three	**0.88**	0.34	2.15
MF			
Visits One, Two and Three	**0.47**	0.19	1.23
Visits One and Two	**0.44**	0.11	1.40
Visits Two and Three	**0.54**	0.18	1.35
SF			
Visits One, Two and Three	**1.01**	0.55	2.15
Visits One and Two	**0.91**	0.51	2.19
Visits Two and Three	**1.08**	0.55	2.15

Table 2. The median (dB) and the accompanying 5th and 95th percentiles (dB) for the distribution of the Systematic influences, of the LF(Ho), of the LF(He), of the MF and of the SF derived from the separate ANOVAs for each of the 41 patients across all three visits, between Visits One and Two and between Visits Two and Three.

The median and the 90% reference intervals (5th and 95th percentiles), estimated using the respective gamma distributions, for the distributions of the MF between each pair of sub-examinations at each of the three visits is shown in Table 3.

Visit	Median (dB)	5th Percentile (dB)	95th Percentile (dB)
One	0.37	0.02	1.26
Two	0.48	0.05	1.82
Three	0.45	0.08	1.26

Table 3. The median (dB) and the accompanying 5th and 95th percentiles (dB) for the distribution of the MF derived from the separate ANOVAs for each of the 41 patients at each of the three visits.

The MF at Visit One as a function of the MD at Visit One is shown in Figure 2, as a function of the classification of the severity of field loss at Visit One in Figure 3 and as a function of the SF at Visit One in Figure 4.

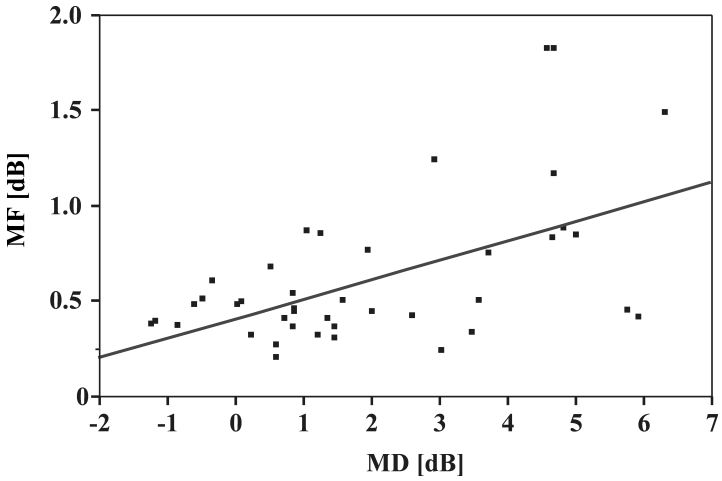

Figure 2. The MF at Visit One as a function of the MD at Visit One for the 41 patients. Note that visual field abnormality is designated by a positive sign. The function exhibits a slope of 0.1 dB in MF per 1.0 dB in MD. (R^2 = 0.30).

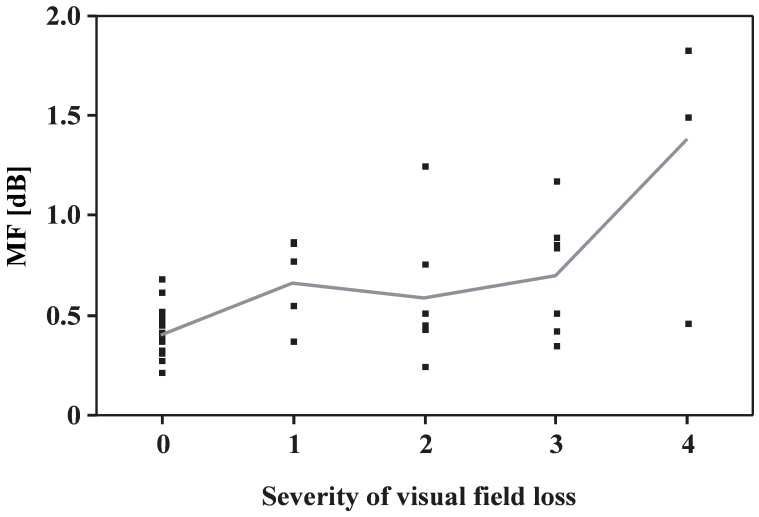

Figure 3. The MF at Visit One as a function of the severity of field loss at Visit One (classified after Hodapp and associates 1993) for the 41 patients. The line connects the mean MF of each group of values of the visual field defect.

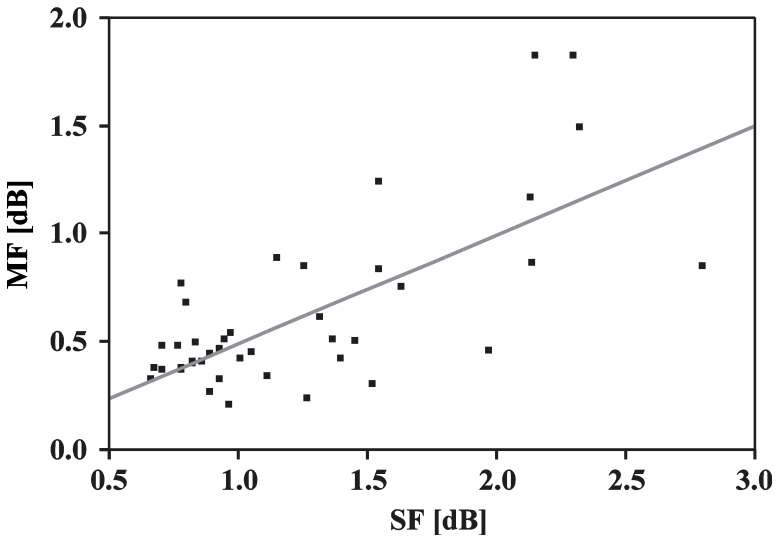

Figure 4. The MF at Visit One as a function of the SF at Visit One for the 41 patients. The function exhibits a slope of 0.5 dB in MF per 1.0 dB in SF (R^2 = 0.49).

The repeatability of the MF for each patient over successive visits is shown in Figure 5 where the difference between the MF at Visit Two and that at Visit One is plotted against the sum of the MF at Visit One and that at Visit Two. The corresponding plot for Visits Two and Three is shown in Figure 6.

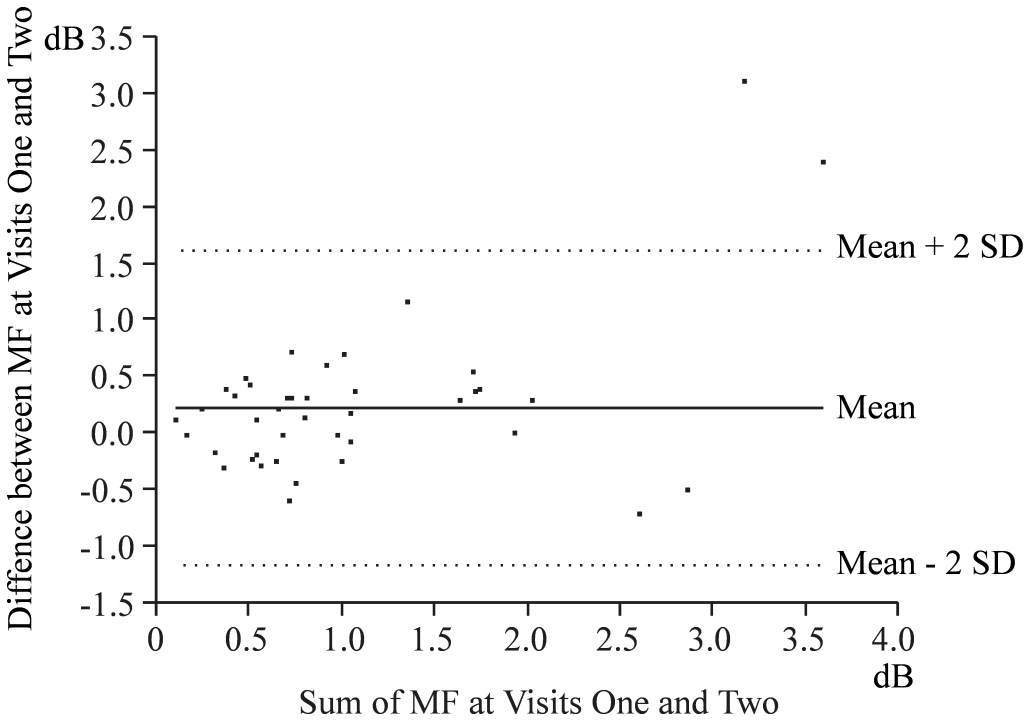

Figure 5. The difference between the MF at Visit Two and at Visit One for each patient by the sum of the both MFs, analogous to the technique of Bland and Altman [54]. The mean of the differences was 0.23 dB (SD 0.69 dB).

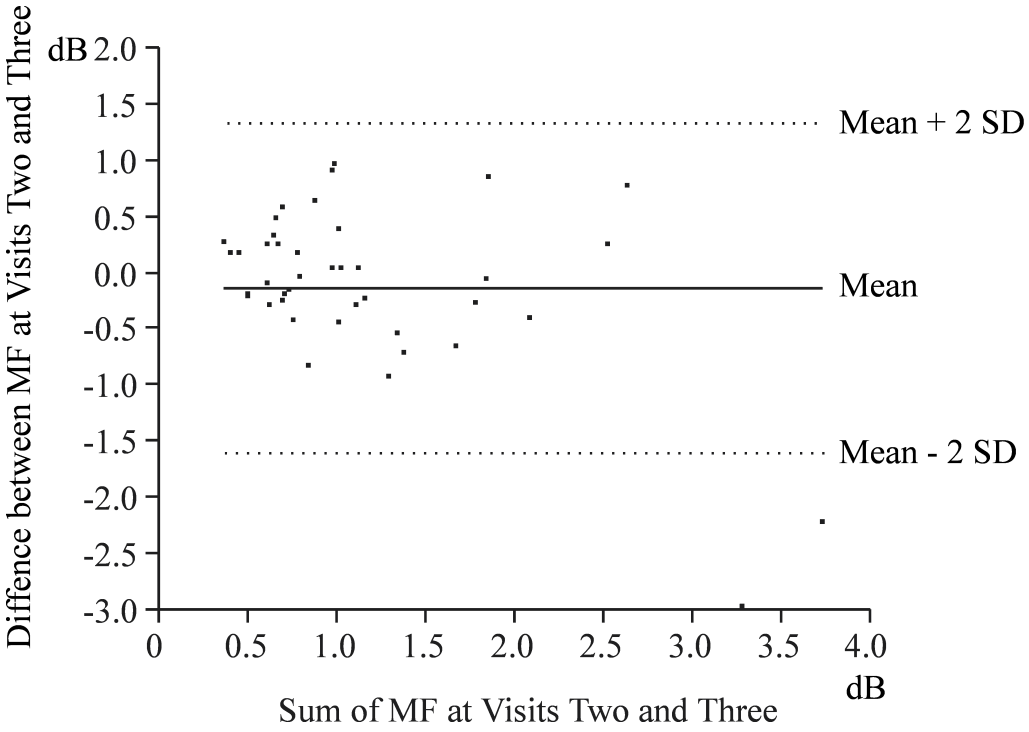

Figure 6. The difference between MF at Visit Three and Two for each patient by the sum of the both MFs, analogous to the technique of Bland and Altman [54]. The mean of the differences was –0.13 dB (SD 0.74 dB).

4. Discussion

The variation in the threshold estimate, both within- and between-examinations, is an inherent part of any psychophysical test and must be considered in the interpretation of the results from a single examination or from a series of visual field examinations, respectively. The presence and extent of this fluctuation is such that a considerable number of follow-up examinations are frequently necessary before progressive visual field loss can be identified [1-5; 55-61]. The study quantifies the contribution of the components of variance associated with the perimetric threshold estimate and describes a new parameter, the Medium-term fluctuation (MF).

The major source (62.0%) of variance present during the visual field examinations in this study was that arising from the Systematic effects. These effects are inevitable in perimetry and seemingly cannot be reduced in magnitude. The second major source (28.5%) of variance arose from the Individual patient-related effects. These effects are also unavoidable since perimetry is currently a subjective test entirely dependent upon the cooperation of the patient. The magnitude of the Systematic and Individual effects therefore renders it essential to minimize the other sources of variance by avoiding potential inaccuracies associated with the examination itself, such as absent or inappropriate refractive correction, and to reduce the influence of less controllable factors, such as the learning and fatigue effects. In addition, the patient should be made aware, as far as possible, of the requirements of perimetry and of the importance of sustained cooperation and attention to the successful outcome.

The LF(Ho) and LF(He), combined, contributed 4.9% of the total variation and the SF 3.8%. The difference in magnitude between the SF, MF and the LF might have been expected to vary as a function of the interval over which the estimation of the given fluctuation was derived. The sub-examinations upon which the MF is based are undertaken within minutes to hours whereas the visits upon which the calculation of the LF is based usually lie months apart [2; 7;

[8; 16; 51; 60]. The magnitude of the LF(He) was greater than that of the MF; however, the magnitude of the LF(Ho) was similar to that of the MF. Both the LF(Ho) and the MF were smaller than the SF. It is interesting to note that the smallest components of variation, namely the LF(Ho) and MF, are estimated in a similar manner. The MF and LF(Ho) arise from the repeated estimation of the threshold at the reference stimulus locations within- and between-visits, respectively. They are independent of the influence of any variation between the reference stimulus locations and are both calculated as homogeneous effects. It would therefore appear that homogenous effects, in general, are smaller than heterogeneous effects. The component of variation summarized in the LF(He) describes the effect arising from the variation between the reference stimulus locations. The LF(He) is likely to be influenced by the extent of the glaucomatous field loss which, itself, leads to greater variation between locations and is the most likely explanation for the greater magnitude of the LF(He) compared to the MF or to the LF(Ho). The separation of the MF into two different components, MF(He) and MF(Ho), which are analogous to the LF(He) and LF(Ho), did not alter the magnitude of the components of variance.

The MF depended approximately linearly on the MD index. The dispersion of the MF increased as the MD increased. As would consequently be expected, a larger MF was also associated with the more severe category of field loss classified in terms of the Hodapp et al [48] grading.

From the mathematics of the analysis of variance (ANOVA), it would be expected that patients with a high total random variance would exhibit large values of both MF and SF. Such an outcome is apparent in the relatively steep slope of the linear regression line between the two parameters (Figure 4): the MF increased by 0.5dB per 1.0dB increase in the SF. Random variance, and consequently the MF, has an upper bound that is approximately proportional to the MD: the MF increases by 0.1dB per 1.0dB increase in MD. This indicates that, not surprisingly, the results of perimetry become less precise as the severity of the field loss increases.

The magnitude and stability of the MF, relative to that of the other components of variance, indicates that the results from two sub-examinations of perimetry

from the same eye can, in general, be combined to form ‘one examination’. It is proposed that the MF should be used as a parameter for reliability between two consecutive visual field examinations, undertaken after a suitable rest period, and should be used in conjunction with those indicating reliability within each examination. The 90% reference interval for the MF across each of the three visits ranged from less than approximately 0.1 dB to less than approximately 1.9 dB (Table 3). When the MF for any two consecutive visual field examinations, undertaken after a suitable rest period, for any given patient with glaucoma lies within the given reference interval, the results from both sub-examinations can be combined thereby facilitating the separation of abnormality and/or of progressive abnormality from the fluctuation in the threshold estimate. A value of MF which lies outside the given upper percentile indicates that the results from the two sub-examinations cannot be regarded as emanating from ‘one’ examination. When the MF lies outside the given reference interval, the results from one or both of the sub-examinations should be called into question. Such an index would be based upon the variability inherent in the stable glaucomatous visual field rather than on the basis of the variability inherent in the normal field.

Calculation of the MF and the LF in this study was limited to the nine stimulus locations common to the grid of both sub-examinations. The use of nine stimulus locations merely samples the extent of the given fluctuation on the assumption that the sampling is representative of the field as a whole. The procedure potentially ignores the influence of the relatively greater variance at the more peripheral locations [14]. In any given patient, the precision of the estimate of the MF or the LF, for the field as a whole, will be affected by the degree of similarity in the position and depth of the field loss for the complete field compared to that manifested at the nine stimulus locations. However, any sampling error derived from using the nine locations is constant between any two visits for any given patient. An alternative would be to increase the number of stimulus locations common to the grid of both sub-examinations. The resulting variance estimate would be more representative of that for the field as

a whole but would be acquired at the expense of an increased examination time with the attendant consequences of an increased fatigue effect.

The magnitudes of the median LF(Ho) (0.57dB for Visits 1 to 3; 0.39dB between Visits 1 and 2; 0.43dB between Visits 2 and 3) and LF(He) (0.93dB for Visits 1 to 3; 0.76dB between Visits 1 and 2; 0.88dB between Visits 2 and 3) were markedly smaller than those of Hutchings and colleagues obtained with the Humphrey Field Analyzer (HFA) and Program 30-2 [LF(Ho) 1.76dB; LF(He) 1.65dB] [7] and more similar to those of Flammer and colleagues with the Octopus perimeter and Program JO [LF(Ho) 0.5dB in normal individuals; 0.9dB in glaucoma suspects; and 1.2dB in OAG. LF(He) 0.2dB in normal individuals; 0.4dB in glaucoma suspects; and 0.5dB in OAG] [50]. The magnitude of the LF(He) compared to the LF(Ho), specified in terms of a ratio, (1.63 for Visits 1 to 3; 1.95 between Visits 1 and 2; 2.05 between Visits 2 and 3) was larger than that of Hutchings and colleagues (1.14) [7], and much higher than that of Flammer and colleagues, (0.64) [50]. The reason for the discrepancies in the values between studies is unclear but is most likely to arise from the differences in the type and severity of the field loss; in the duration of the follow-up; in the thresholding algorithms; in the number, and position, of stimulus locations at which a double determination of sensitivity is undertaken; and in the stimulus parameters of the instruments.

5. Conclusion

In this study, a new parameter of variability of perimetric examinations, namely the medium-term fluctuation (MF), is introduced and quantified concerning its contribution to the total variation of threshold estimate. The MF describes the variability occurring between two perimetric examinations that are carried out in an interval of minutes to hours at the same day. Furthermore, the distribution of the MF and its relation to the summary visual field indices were computed.

As a compromise between high spatial resolution (for best detection of small areas of new or progressive field loss) and short duration of the examination (thereby reducing fatigue effects), the method of concentrating the stimulus locations in given Regions Of Interest (ROI) and splitting the gained grid into two single sub-examinations has been established. In order to allow interpretation of the results of these examinations, the fluctuation between the two sub-examinations (i.e. the MF) has to be analyzed.

41 eyes of 41 volunteer patients with stable open angle glaucoma (OAG) had been examined with the instrument of fundus-oriented perimetry (FOP) on the Tübingen Computer Campimeter (TCC) in this study. Each visit of each patient consisted of two sub-examinations, undertaken after a rest period, each with a separate stimulus grid within 30° eccentricity. Nine stimulus locations were common to both grids. The procedure was repeated after 224 ± 80 days (mean ± SD) and again after a further 228 ± 62 days. Stimuli that subtended 0.431° (Goldmann III) were presented on a video display unit with a background luminance of 10cdm^{-2} within the central 30° visual field. A modified 4-2-1-1 dB staircase strategy with 4 reversals of threshold and maximum-likelihood estimation using custom software were used to estimate the threshold of the light differentiation sensitivity (LDS). MF was calculated for the nine common reference locations from each pair of sub-examinations using a multiple-factor analysis of variance (ANOVA). Additionally, the short-term fluctuation (SF) and the homogenous (LF[Ho]) and heterogeneous (LF[He]) long-term fluctuation were determined.

The contribution of the MF was the smallest of all computed components and made for 1.1% of the total variation. The Standard Deviation of this effect in the ANOVA was 0.72 dB. Compared with the known components of variation, namely short-term (SF) and long-term fluctuation with its components LF(Ho) and LF(He), MF was markedly smaller. SF, LF(Ho) and LF(He) contributed 3.8% (1.35 dB), 1.2% (0.74 dB) and 3.8% (1.34 dB) of the total variation. Systematic influences (eccentricity and position of the reference locations in the visual field) accounted for 61.7%. Individual influences (age, gender, etc.) contributed 28.5%.

The median of the frequency distribution of the MF over all three visits was the minimum of all computed, too, and equaled 0.47 dB (90% Reference Interval: 0.19 dB – 1.23 dB). SF: 1.01 dB (0.55 dB – 2.15 dB); LF(Ho): 0.57 dB (0.14 - 1.44 dB); LF(He): 0.93 dB (0.49 - 2.20 dB).

This results prove that the technique of splitting one high-resolution grid into two sub-examinations is legitimate, since the outcome of the perimetric examination is not biased in a relevant manner by MF.

The good stability of the MF is best shown by the use of the 90% Reference Interval for the distributions of the MF for each patient between each pair of sub-examinations at each of the three visits, ranging from 0.02 dB to 1.82 dB. As a consequence, in cases with MF exceeding the upper limit, the two sub-examinations cannot be regarded as originating from one examination. In this terms, MF should be used as a reliability index between two visual field examinations to be able to repeat examinations where necessary.

Concerning the relationship of the MF to the summary visual field indices, the MF depended approximately linearly on the MD index (slope of 0.1 dB in MF per 1.0 dB in MD, $R^2 = 0.30$) and was also strongly associated with the category of field loss according to Hodapp et al. These results and a simple linear regression analysis between the MF and the SF (slope of 0.5 dB in MF per 1.0 dB in SF, $R^2 = 0.49$) showed that in visual fields with more severe loss, the outcome of perimetry was less precise.

In the current study, the MF was illustrated in the context of high-resolution perimetry; however, it is applicable to all algorithms and types of perimetry, including the SITA algorithms for standard automated perimetry and for short wavelength perimetry [62-63] and also the threshold algorithm for Frequency Doubling perimetry [64-68] and the perimeter manufacturers should be encouraged to derive the appropriate reference intervals and to implement the requisite software in their instruments.

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