Aging effects in psychophysical foveal light detection sensitivity

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Abstract: Foveal light detection sensitivity was evaluated in 348 volunteers covering a large age range using an automated perimetry performed in the Humphrey Field Analyzer II. Foveal sensitivity was measured using the Humphrey's 4–2 bracketing strategy with a 30 dB initial stimulus intensity, at an inferior visual field location, a 0.431 (4mm^2, viewed at 30 cm; Goldmann III) spot of white light is presented on a 10 cd/m2 white background. The sensitivity measurement was performed monocularly in both eyes randomly chosen. Our results showed a negative moderate correlation between age and the light sensitivity detection of OD (r= -0.5591; p< 0.001) and OS (r= -0.6021, p< 0.001). A moderate positive correlation was obtained between the light sensitivity of the two eyes (r= -0.5986; p< 0.001). We conclude reporting aging effect in the foveal sensitivity light detection suggesting functional decrease in perceptual function guide by developmental changes. Tolerance limits for normative purposes were measured.

Keywords: Foveal Sensitivity; Visual Perception; Clinical Psychophysics; Aging; Automated Perimetry

1. Introduction

Foveal sensitivity to brightness is one of the most basic visual functions related to the central vision since it is related to simple light detection in a static perimetry protocol [1]. Despite being a simple task, there is a high probability missed responses, either positive or false negative errors, either by loss of fixation to the central target. Those missed responses had a very negative impact on the visual field result increasing the damage area or intensity [2, 3].

In the clinical application of the visual field perimetry, normative values of the brightness are useful to compare subjects with diseases and for diagnosis purposes. Visual field brightness sensitivity perimetry is used as the main diagnostic tool in glaucoma [4-7]. Important contributions of the perimetry are related to the understanding functional impairment related to retina damage caused by other eye diseases including aged-related macular degeneration [8], optical neuropathies [9-13] systemic diseases like diabetes [14] or in drug intoxication by hydroxychloroquine [15-17], vigabatrin [18], tamoxifen [19] and mercury vapor intoxication [20].

Those related impairment are almost all regarding to the peripheral visual field scotomas or constrictions. No foveal sensitivity is reported and the studies assuming that the normative values embedded in the system is reliable for all subjects. Considering the absence of studies of foveal sensitivity to brightness detection, the aim of our study is to describe normative data for a large age range of ages. These data also can contribute to the understanding of the aging effect in this perceptual function.

2. Methods

2.1. Subjects

We evaluated 348 volunteers we evaluated 348 volunteers who were performing routine eye exams and did not have any ocular disease in the Pacaembu Eye Clinic. They were grouped according to their age in 13 groups ranging from 15-85 years. See demographic details in Table 1.

Inclusion criteria were that participants had to have Snellen visual acuity of 20/20 or better, an absence of oph-

thalmologic disease or diseases that affect the visual system (i.e. diabetes, multiple sclerosis), and had to be non smokers. Subjects with history of alcoholism, occupational exposure to toxic substances or with congenital color vision deficiencies were excluded. All subjects underwent a complete ophthalmologic examination and anamnesis.

Informed consent was obtained from all subjects. The procedures complied with the tenets of the Declaration of Helsinki and were approved by the Ethics Committee of the Pacaembu Eye Clinic.

2.2. Equipment and Procedures

There are different methods to perform measurement of visual field sensitivities such as manual kinetic perimetry using a Goldmann perimeter that allows analysis of the entire visual field, and automated static perimetry that provides a reliable, accurate, and reproducible method of visual field testing, but is restricted to 30.1 or 60.1. In the present study, we used the Humphrey Field Analyzer II-model 750i (Humphrey Instruments, San Leandro, California, USA) to measure light sensitivity against a contrast-illuminated background. The standard automated perimetry (SAP) utilizes the Swedish Interactive Threshold Algorithm (SITA) using the central 30-2 strategy. Foveal sensitivity was measured using the Humphrey's 4–2 bracketing strategy with a 30 dB initial stimulus intensity. At a inferior visual field location, a 0.431 (4mm^2, viewed at 30 cm; Goldmann III) spot of white light is presented on a 10 cd/m2 white background for 200 ms inside a "diamond" shape built by four small high intensity lights.

Table 1. Demographic data of the volunteers

		Age-range	Gender Distribution	Light Sensitivity OD	Light Sensitivity OS
Group 1	n= 21	15-25*	12 M; 9 F#	38.1 (1.22)$	38.0 (1.55)
Group 2	n= 30	26-30	10 M; 20 F	37.8 (1.96)	38.3 (1.82)
Group 3	n= 30	31-35	13 M; 17 F	37.8 (1.64)	37.4 (2.15)
Group 4	n= 30	36-40	11 M; 19 F	37.2 (1.49)	37.5 (1.40)
Group 5	n= 30	41-45	12 M; 18 F	37.0 (1.75)	37.1 (1.58)
Group 6	n= 30	46-50	14 M; 16 F	36.7 (1.79)	36.9 (1.32)
Group 7	n= 30	51-55	12 M; 18 F	36.3 (1.02)	36.2 (1.38)
Group 8	n= 30	56-60	10 M; 20 F	36.2 (1.37)	36.4 (2.04)
Group 9	n= 30	61-65	11 M; 19 F	36.2 (1.53)	35.4 (1.71)
Group 10	n= 30	66-70	12 M; 18 F	35.6 (1.69)	35.4 (2.23)
Group 11	n= 30	71-75	12 M; 18 F	35.4 (1.37)	34.9 (1.87)
Group 12	n= 18	76-80	5 M; 13 F	34.1 (1.96)	33.9 (1.45)
Group 13	n= 09	81-90	03 M; 06 F	33.8 (1.53)	32.3 (2.34)

* Age range in years.
# M= male; F= female.
$ values in dB; mean (standard deviation).

All observers were optically corrected for the test distance. The observer's task was to press a button to indicate the presence of the light spot whenever it was detected. Visual field locations of reduced sensitivity relative to con-

trols required brighter stimuli to reach threshold, and had lower decibel (dB) sensitivity values. Similarly, higher dB values represented more sensitive retinal locations (where 1dB ¼ 0.1 log unit). Sequences of test stimuli were presented randomly throughout the entire visual field, and the sensitivity at each location was determined by the standard Humphrey staircase procedure: the spot intensity was increased in steps of 4 dB until the patient responded with a 'yes' (seen), then it was decreased in steps of 2 dB until the patient responded 'no' (not seen). After two such reversals, the visual threshold was calculated as the average of the four measurements.

The SITA program used in the SAP test reduces test time by approximately 50% when compared with the full threshold program used in SWAP test, because the number of stimuli presented is 29% smaller in normal fields [21, 22]. It is a more reliable psychophysical paradigm to measure localized threshold. Reliability and efficiency of the SITA algorithm is enhanced by (1) use of information about surrounding points, (2) use of information about threshold values in age-matched controls, (3) reacting to changes in the pacing of the test, (4) elimination of retest trials for the 10 points used to calculate short-term fluctuation in the full threshold algorithm used in SWAP, (5) an improved method of evaluating false positive and false negative reliability parameters, and (5) use of a maximum likelihood procedure for 18–20 estimates of threshold [21].

2.3. Statistical Analysis

The results were analyzed with the program Stastistica 11.0 (StatSoft, Inc., Tulsa, USA). Statistical analysis was performed on the data from the two eyes of each subject, and the first eye tested was randomly chosen. Full descriptive statistical was performed and the normality distribution of the data was checked by the Kolmogorov-Smirnov & Lilliefors test. We used the Repeated Measurement ANOVA Test to compare the sensitivity data between groups and gender with a post-hoc Fisher LSD test for group discriminability. For the correlation study, we used the Pearson R correlation coefficient. In all analyses, p-values < 0.05 were considered to be statistically significant.

Tolerance limits were calculated for normative purposes according to the equation 1.

$$\text{Tolerance Limits} = \text{Mean} \pm (K*SD) \qquad \text{(eq. 1)}$$

in which K is a multiply factor based in the sample size and the population coverage at a certain confidence level and SD is the standard deviation [23]. In our study, we create tolerance limits covering 95% of the population with a confidence of 95%, using a K factor of 2.549.

3. Results

We tested for significant differences the light detection sensitivity. Statistical differences were found between groups for both visual field sensitivity in OD and OS (F=

13.9, p< 0.001 and F= 17.9, p< 0.001, respectively). Group differences were found between groups 1, 2 and 3 with the older groups; groups 4 to 6 differing from the youngest and oldest groups; groups 7 to 11 also differing from the youngest and oldest groups; and finally, the groups 12 and 13 have different sensitivity than the youngest groups. The difference indicates a reduction in sensitivity from the youngest to oldest groups but with similar values in both eyes (Figure 1). No gender differences were found in any group.
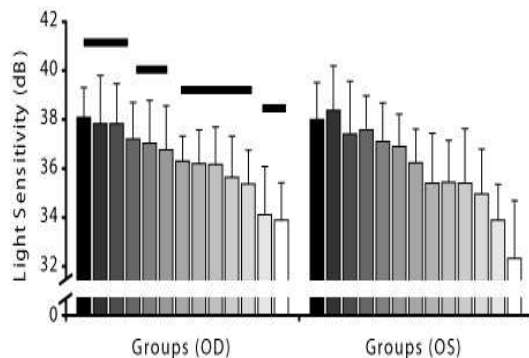

Figure 1. Mean and standard deviation of the light detection sensitivity measures for OD and OS. De columns are the groups from G1 (15-25 yrs – in black) to G13 (81-90 yrs – in white). The black brackets on the upper side shows the range

There is a significant negative correlation between age and light detection sensitivity values for OD (r= -0.5591, p< 0.001) and OS (r= -0.6021, p< 0.001) (Figure 2).
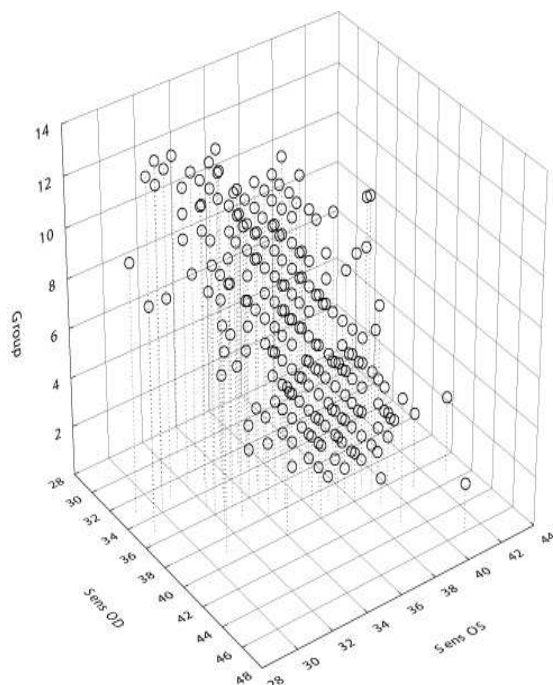

Figure 2. Tree dimension scatter plot of foveal sensitivity from OD and OS correlated with age (scaling plotted as group). Each circle is a volunteer result.

Correlation between the eyes was studied and a moderate to high coefficient was obtained (r= -0.5986, p< 0.001) (Figure 3).
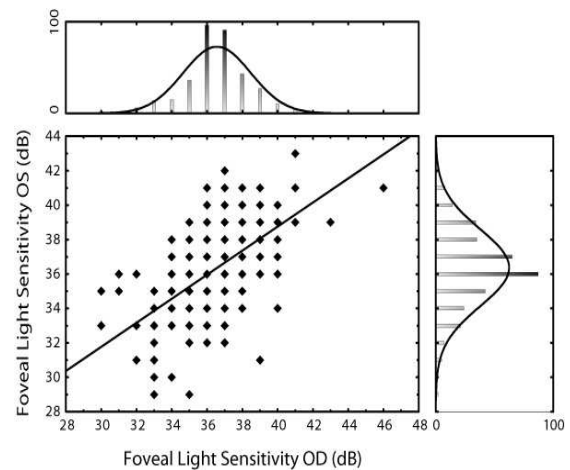

Figure 3. Correlation between the sensitivities measured fro OD and OS for all age ranges. Statistical analysis showed a moderate correlation. Data shows a normal distribution with an overall ages sensitivity mean between 35 to 38 dB.

Tolerance limits were obtained for each age group. Superior and inferior tolerance limits were shown in Figure 4.
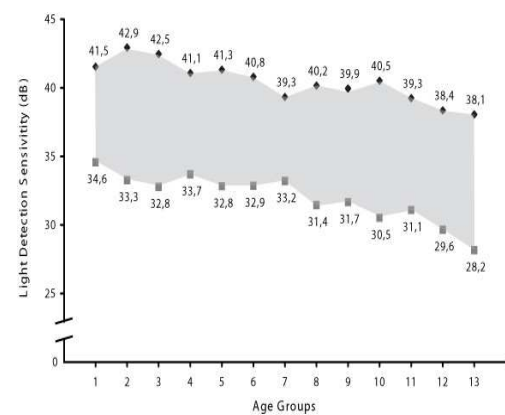

Figure 4. Tolerance Limits of the foveal light sensitivity detection for clinical application. The gray area is the normality range between the upper and the lower normality values presented near the points for each age group.

4. Discussion

Foveal sensitivity to light detection was successfully measured and shown aging effect that should be considered for diagnosis and clinical studies purposes. As we know, this is the first developmental study evaluating this basic visual function even with the perimetry had been used at decades for analyze visual perception.

The aging effect was very robust and could evidence at least four periods of reduction in sensitivity to light detection. The first period separate the youngest three groups, suggesting that the sensitivity remains unchanged up to thirty years. At this age there is a significant reduction in sensitivity that has similar detection ability that last for the next three decades. The third period of reduction in sensitivity occurs at the beginning of the sixties and the last reduction around the eighties.

The relative sparse periods between the first three stages of sensitivity could be explained by the function measured and by the psychophysical paradigm used. Light detection could be considered the simplest perception function. Both the stimulus and the observer task are very basic which means a low level function in the hierarchical visual information processing. The stimuli used are frequently a spot of light of high intensity [1, 24]. We can argue that a very suprathreshold intensity and with low spatial and temporal complexity stimuli suggest a poorer sensitivity to measure small differences and lower reliability [25]. In our case, that was reflected as difficult in detecting small changes by aging grouping subjects with ages ranging in 15-30 years. The second point that probably contribute to decrease the sensitivity in detect aging changes is regarding to the psychophysical task used, knowing as Yes-No paradigm. The subject had two possible responses to signalize their perception. Pressing a button the system record as "yes" responses and no answer are interpreted as "no" responses. However, this simplest psychophysical paradigm, even under an adaptative staircase procedure, are well know to show high variability and mainly if "no" responses are recorded in the initial steps of tenting [26-30].

Asymmetry responses between the eyes were confirmed by a moderate correlation coefficient in our sample. The possible origins of the asymmetrical response could be physiological or regarding to the psychophysical task. Even in normal subjects the eyes differing from each other in many aspects. Probably the most influent should be the optical physiology. Normal subjects exhibits differences in their optical surfaces creating optical aberrations that are unique for that eye [31]. The presence of optical aberration differences generates small changes in eye's sensitivity and could support the moderate correlation found in our sample.

The psychophysical paradigm used for foveal light detection sensitivity is also a source of variation that has to be considered. The staircase steps and routine used by SITA our Full-Threshold strategies measured significant different thresholds of 34.8dB and 33.3dB, respectively [32]. However, in our study, we obtained a moderate asymmetry using the same strategy suggesting that other parameter of the psychophysical test could also been negatively interfering in the sensitivity measurement. The staircase step in foveal measurement is a 4/2 double bracketing strategy, in which initial steps coming from the suprathreshold intensities are presented reducing a 4dB intensity after each "yes" response". After a negative response, the intensities are increased in 2dB intensity until another "yes" response be recorded. Threshold is calculated as the mean value of the last "no" and "yes" responses. Since there is no much levels and repetitions tested, a wrong "no" response in the beginning of the test could remain the intensities in suprathreshold levels decreasing the sensitivity measured.

Experience and training could also be another variance font. We addressed these questions and in another study that we are conducting shows a better performance in the second foveal measurement but with no learning effect (paper submitted).

We could not find studies focused in the developmental aspects of the light sensitivity detection. It was surprising since the perimetry is the main functional test related to the diagnosis of very frequent and important ocular disease, the glaucoma [5-7, 33-36] but also in other retina impairment as in the diabetes [37-41], multiple sclerosis [10, 42-44], mercury intoxication [20, 45], and drug intoxications with hydroxichloroquine [16, 46-49], vigabatrin [18, 50] and others. A possible explanation could be since glaucoma initially shows periphery reductions in visual field the authors were much more interested and focused in study those alterations than the central ones. One work found a mild reduction in the foveal sensitivity in glaucoma in 15/35 patients evaluated but no values were present by the authors [51]. We found one study reporting quantitative reduction values for foveal light detection sensitivity in subjects with Leber's Hereditary Optical Neurophaty (LHON) [52]. Those authors reported a reduction in the foveal sensitivity ranging from 2.7 to 10.3dB compared to the baseline. Thus, we believe that our work cover a relevant gap in the visual field and perceptual development literature.

Recent studies in glaucoma are using additionally to the white-to-white strategy a blue-yellow strategy in perimetry [53-55]. Some studies have been reported that the perimetry using blue stimulus on a yellow background, isolating the S-cone pathway [56]could anticipate the impairment 3 to 5 years than using the white-on-white strategy even with the high asymmetry in retina quadrants when compared with the traditional stimulus [56]. Another relevant point to be stressed here is that those studies are replicating the visual field strategies, evaluating the periphery of visual fields with no attention to possible central defects only detected by the foveal measurement.

Tolerance limits for different ages were calculated for clinical purposes since no study was found to analyze the development of this basic visual function. We found to be three cores of sensitivity levels that are more or less stable over their range suggesting a more stepped than a continuous functional decrease. Our first core ends around the 35 yrs with a mean sensitivity of 38dB. The second core covers the ages from 36 to 65yrs, with a mean sensitivity of 35dB and the last core isolated the older patients with a mean foveal sensitivity of 33dB. It is interesting to note that the sensitivity to light detection reduces an average of 5dB that means a half logarithmic unit, a very subtle reduction but with strong negative impact in visual functions [57].

It is important to know how the sensitivity function develops during the lifespan since many visual and ocular diseases that affects the central vision occurs with the aging and are increasingly frequent after the age of forty's. These normality values should be checked in the patients with doubt central vision diagnosis as age-related macular degeneration [58], multiple sclerosis neuropathy [59], diabetic retinopathy [37], intoxications [20] and for a more controlled study of the early foveal involvement in glaucoma patients [51].

We conclude reporting aging effect in the foveal sensitivity light detection measured psychophysically suggesting functional decrease in perceptual function guide by developmental changes. Our tolerance limits could be used by clinicians as normative data in developmental studies or diagnostic procedures.

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References

[1] H.Bebie, F.Fankhauser, J.Spahr. Static perimetry: strategies, Acta Ophthalmol. (Copenh) 54 (1976) 325-338.

[2] M.A.Cascairo, W.C.Stewart, S.E.Sutherland. Influence of missed catch trials on the visual field in normal subjects, Graefes Arch. Clin. Exp. Ophthalmol. 229 (1991) 437-441.

[3] F.Fankhauser. Influence of missed catch trials on the visual field in normal subjects, Graefes Arch. Clin. Exp. Ophthalmol. 231 (1993) 58-59.

[4] D.C.Hood. Relating retinal nerve fiber thickness to behavioral sensitivity in patients with glaucoma: application of a linear model, J. Opt. Soc. Am. A Opt. Image Sci. Vis. 24 (2007) 1426-1430.

[5] R.K.Parrish, S.J.Gedde, I.U.Scott, W.J.Feuer, J.C.Schiffman, C.M.Mangione, A.Montenegro-Piniella. Visual function and quality of life among patients with glaucoma, Arch. Ophthalmol. 115 (1997) 1447-1455.

[6] P.A.Sample, C.F.Bosworth, R.N.Weinreb. The loss of visual function in glaucoma, Semin. Ophthalmol. 15 (2000) 182-193.

[7] R.L.Stamper. Psychophysical changes in glaucoma, Surv. Ophthalmol. 33 Suppl (1989) 309-318.

[8] P.V.Algvere, L.Berglin, P.Gouras, Y.Sheng. Transplantation of fetal retinal pigment epithelium in age-related macular degeneration with subfoveal neovascularization, Graefes Arch. Clin. Exp. Ophthalmol. 232 (1994) 707-716.

[9] M.I.Boone, G.G.Massry, R.A.Frankel, J.B.Holds, S.M.Chung. Visual outcome in bilateral nonarteritic anterior ischemic optic neuropathy, Ophthalmology 103 (1996) 1223-1228.

[10] S.J.Givre, D.C.Hood, M.Wall, R.H.Kardon. Comparison of threshold and multifocal-vep perimetry in recovering and recovered optic neuritis, Investigative Ophthalmology & Visual Science 41 (2000) S625.

[11] D.R.Johns, K.H.Smith, N.R.Miller, M.E.Sulewski, W.B.Bias. Identical-Twins Who Are Discordant for Leber Hereditary Optic Neuropathy, Archives of Ophthalmology 111 (1993) 1491-1494.

[12] Y.Rotenstreich, G.A.Fishman, M.Lindeman, K.R.Alexander. The application of chromatic dark-adapted kinetic perimetry to retinal diseases, Ophthalmology 111 (2004) 1222-1227.

[13] H.Terasaki, Y.Miyake, R.Nomura, M.Horiguchi, S.Suzuki, M.Kondo. Blue-on-yellow perimetry in the complete type of congenital stationary night blindness, Invest Ophthalmol. Vis. Sci. 40 (1999) 2761-2764.

[14] J.C.Brown, J.A.Kylstra, M.L.Mah. Entoptic perimetry screening for central diabetic scotomas and macular edema, Ophthalmology 107 (2000) 755-759.

[15] M.Mavrikakis, S.Papazoglou, P.P.Sfikakis, G.Vaiopoulos, K.Rougas. Retinal toxicity in long term hydroxychloroquine treatment, Ann. Rheum. Dis. 55 (1996) 187-189.

[16] S.A.Mazzuca, R.Yung, K.D.Brandt, R.D.Yee, B.P.Katz. Current practices for monitoring ocular toxicity related to hydroxychloroquine (Plaquenil) therapy, J. Rheumatol. 21 (1994) 59-63.

[17] M.R.Razeghinejad, F.Torkaman, H.Amini. Blue-yellow perimetry can be an early detector of hydroxychloroquine and chloroquine retinopathy, Med. Hypotheses 65 (2005) 629-630.

[18] J.McDonagh, L.J.Stephen, F.M.Dolan, S.Parks, G.N.Dutton, K.Kelly, D.Keating, G.J.Sills, M.J.Brodie. Peripheral retinal dysfunction in patients taking vigabatrin, Neurology 61 (2003) 1690-1694.

[19] A.Eisner, D.F.Austin, J.R.Samples. Short wavelength automated perimetry and tamoxifen use, Br. J. Ophthalmol. 88 (2004) 125-130.

[20] M.T.Barboni, M.F.da Costa, A.L.Moura, C.Feitosa-Santana, M.Gualtieri, M.Lago, M.A.Medrado-Faria, L.C.Silveira, D.F.Ventura. Visual field losses in workers exposed to mercury vapor, Environ. Res. 107 (2008) 124-131.

[21] B.Bengtsson, J.Olsson, A.Heijl, H.Rootzen. A new generation of algorithms for computerized threshold perimetry, SITA, Acta Ophthalmol. Scand. 75 (1997) 368-375.

[22] B.Bengtsson, A.Heijl, J.Olsson. Evaluation of a new threshold visual field strategy, SITA, in normal subjects. Swedish Interactive Thresholding Algorithm, Acta Ophthalmol. Scand. 76 (1998) 165-169.

[23] W.J.Dixon, F.J.Massey. Introduction to Statistical Analysis, McGraw-Hill, New York, N.Y., 1969.

[24] L.F.Jindra. Theoretical methods in the assessment of vision and automated perimetry, Ophthalmic Surgery Lasers & Imaging 37 (2006) 516-523.

[25] L.C.Norden. Reliability in perimetry, J. Am. Optom. Assoc. 60 (1989) 880-890.

[26] G.H.Thomson. A new point of view in the interpretation of threshold measurements in psychophysics, Psychological Review 27 (1920) 300-307.

[27] S.S.Stevens. Problems and methods of psychophysics, Psychol. Bull. 55 (1958) 177-196.

[28] J.A.Swets. Detection Theory and Psychophysics - A Review, Psychometrika 26 (1961) 49-63.

[29] P.Bovet. Method of Absolute Judgement in Psychophysics, Bulletin de Psychologie 22 (1969) 631-639.

[30] F.W.Fitzke. Clinical psychophysics, Eye 2 Suppl (1988) S233-S241.

[31] D.J.Risovic, K.R.Misailovic, J.M.Eric-Marinkovic, N.G.Kosanovic-Jakovic, S.M.Milenkovic, L.Z.Petrovic. Refractive errors and binocular dysfunctions in a population of university students, Eur. J. Ophthalmol. 18 (2008) 1-6.

[32] R.B.Schimiti, R.R.Avelino, N.Kara-Jose, V.P.Costa. Full-threshold versus Swedish Interactive Threshold Algorithm (SITA) in normal individuals undergoing automated perimetry for the first time, Ophthalmology 109 (2002) 2084-2092.

[33] R.S.Anderson. The psychophysics of glaucoma: improving the structure/function relationship, Prog. Retin. Eye Res. 25 (2006) 79-97.

[34] E.A.Ansari, J.E.Morgan, R.J.Snowden. Glaucoma: squaring the psychophysics and neurobiology, Br. J. Ophthalmol. 86 (2002) 823-826.

[35] S.Kogure, T.Chiba, S.Saito, H.Iijima, S.Tsukahara. Predicting glaucomatous sensitivity loss using perimetric color saturation test, Jpn. J. Ophthalmol. 47 (2003) 537-542.

[36] P.Pearson, W.H.Swanson, R.L.Fellman. Chromatic and achromatic defects in patients with progressing glaucoma, Vision Res. 41 (2001) 1215-1227.

[37] B.Bengtsson, K.J.Hellgren, E.Agardh. Test-retest variability for standard automated perimetry and short-wavelength automated perimetry in diabetic patients, Acta Ophthalmol. 86 (2008) 170-176.

[38] G.H.Bresnick, V.Smith, J.Pokorny. Visual function abnormalities in macular heterotopia caused by proliferative diabetic retinopathy, Am. J. Ophthalmol. 92 (1981) 85-102.

[39] F.Mori, S.Ishiko, N.Kitaya, T.Hikichi, E.Sato, A.Takamiya, A.Yoshida. Use of scanning laser ophthalmoscope microperimetry in clinically significant macular edema in type 2 diabetes mellitus, Jpn. J. Ophthalmol. 46 (2002) 650-655.

[40] R.Nomura, H.Terasaki, H.Hirose, Y.Miyake. Blue-on-yellow perimetry to evaluate S cone sensitivity in diabetics, Ophthalmic Res. 32 (2000) 69-72.

[41] M.Okuyama, S.Okisaka. Automatic static threshold perimetry is useful for estimating the effects of laser photocoagulation on diabetic maculopathy, Ophthalmic Res. 30 (1998) 207-215.

[42] N.Accornero, S.Rinalduzzi, M.Capozza, E.Millefiorini, G.C.Filligoi, L.Capitanio. Computerized color perimetry in multiple sclerosis, Mult. Scler. 4 (1998) 79-84.

[43] H.Cheng, M.Laron, J.S.Schiffman, R.A.Tang, L.J.Frishman. The relationship between visual field and retinal nerve fiber layer measurements in patients with multiple sclerosis, Invest Ophthalmol. Vis. Sci. 48 (2007) 5798-5805.

[44] T.Vidovic, B.Cerovski, D.H.Vidovic, J.Cerovski, K.Novak-Laus. Inapparent visual field defects in multiple sclerosis patients, Coll. Antropol. 29 Suppl 1 (2005) 67-73.

[45] J.Lebel, D.Mergler, M.Lucotte, M.Amorim, J.Dolbec, D.Miranda, G.Arantes, I.Rheault, P.Pichet. Evidence of early nervous system dysfunction in Amazonian populations exposed to low-levels of methylmercury, Neurotoxicology 17 (1996) 157-167.

[46] M.Easterbrook. Detection and prevention of maculopathy associated with antimalarial agents, Int. Ophthalmol. Clin. 39 (1999) 49-57.

[47] W.M.Hart, Jr., R.M.Burde, G.P.Johnston, R.C.Drews. Static perimetry in chloroquine retinopathy. Perifoveal patterns of visual field depression, Arch. Ophthalmol. 102 (1984) 377-380.

[48] R.K.Maturi, M.Z.Yu, R.G.Weleber. Multifocal electroretinographic evaluation of long-term hydroxychloroquine users, Archives of Ophthalmology 122 (2004) 973-981.

[49] S.A.Mazzuca, R.Yung, K.D.Brandt, R.D.Yee, B.P.Katz. Common Practices for Monitoring Ocular Toxicity Related to Hydroxychloroquine (Plaquenil) Therapy, Journal of Rheumatology 21 (1994) 59-63.

[50] I.G.Rennie. Clinically important ocular reactions to systemic drug therapy, Drug Saf 9 (1993) 196-211.

[51] J.L.Anctil, D.R.Anderson. Early foveal involvement and generalized depression of the visual field in glaucoma, Arch. Ophthalmol. 102 (1984) 363-370.

[52] N.J.Newman, V.Biousse, S.A.Newman, M.T.Bhatti, S.R.Hamilton, B.K.Farris, R.L.Lesser, R.E.Turbin. Progression of visual field defects in leber hereditary optic neuropathy: experience of the LHON treatment trial, Am. J. Ophthalmol. 141 (2006) 1061-1067.

[53] J.Felius, W.H.Swanson. Effects of cone adaptation on variability in S-cone increment thresholds, Invest Ophthalmol. Vis. Sci. 44 (2003) 4140-4146.

[54] A.Serra, I.Zucca, A.Tanda, V.Piras, M.Fossarello. Blue-yellow perimetry in patients with ocular hypertone, Acta Ophthalmol. Scand. Suppl (1998) 24-27.

[55] M.G.Uva, P.M.Di, A.Longo, K.Lauretta, M.Reibaldi, A.Reibaldi. Pattern ERG and RNFL thickness in hypertensive eyes with normal blue-yellow visual field, Graefes Arch. Clin. Exp. Ophthalmol. (2012).

[56] L.Racette, P.A.Sample. Short-wavelength automated perimetry, Ophthalmol. Clin. North Am. 16 (2003) 227-vii.

[57] L.N.Thibos. Acuity perimetry and the sampling theory of visual resolution, Optometry and Vision Science 75 (1998) 399-406.

[58] I.Cacho, C.M.Dickinson, B.C.Reeves, R.A.Harper. Visual acuity and fixation characteristics in age-related macular degeneration, Optom. Vis. Sci. 84 (2007) 487-495.

[59] L.Vleugels, M.Charlier, A.van Nunen, C.Lafosse, R.Vogels, P.Ketelaer, E.Vandenbussche. Temporal resolution deficits in the visual fields of MS patients, Vision Research 39 (1999) 2429-2438.