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MIGUEL DE OLIVEIRA TAVARES MENDES RAIMUNDO

PADRÕES DE DANO NAS VIAS DE PROCESSAMENTO DE MOVIMENTO, COR E CONTRASTE ACROMÁTICO AO LONGO DA HISTÓRIA NATURAL DO GLAUCOMA

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“How can a three-pound mass of jelly that you can hold in your palm imagine angels, contemplate the meaning of infinity, and even question its own place in the cosmos?”

Vilayanur S. Ramachandran

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Nesta fase final da minha formação académica e olhando para trás, é inevitável nomear algumas pessoas às quais não posso deixar de prestar o devido reconhecimento.

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A todos, o meu obrigado!

RESUMO

Objectivo. Com este trabalho pretendeu-se clarificar três questões importantes na fisiopatologia do glaucoma: (1) se os padrões de dano nas vias de processamento de movimento, contraste acromático e contraste cromático evoluem de forma similar na história natural do glaucoma; (2) se o dano que ocorre precocemente no glaucoma é específico para as vias de grandes células ganglionares e (3) se existem padrões de dano relacionados com a excentricidade ao longo da evolução da doença.

Métodos. Estudámos uma coorte de 41 participantes divididos em grupos diferentes (9 controlos, 13 hipertensos oculares, 12 suspeitos de glaucoma e 7 doentes de glaucoma) através de uma análise de correlação de dano psicofísico com a progressão da doença. Testámos diferentes vias visuais usando três novos testes psicofísicos que obrigam à comparação e discriminação de um atributo visual (movimento, contraste acromático e contraste cromático nos eixos dos cones L, M e S) entre dois pontos separados em movimento.

Resultados. Obtivemos uma correlação significativa com a progressão da doença em todos os testes e conseguimos discriminar grupos de sujeitos inclusive em estádios precoces (p. ex. hipertensão ocular *vs* controlos). Encontrámos padrões de dano relacionados com a excentricidade, com uma perda linear de desempenho do centro para a periferia notória no grupo de hipertensos oculares.

Conclusões. Concluímos que os padrões de dano ao longo da história natural da doença evoluem de forma similar nas vias de processamento de movimento, contraste acromático e contraste cromático e que não são específicos das vias de grandes células ganglionares. O desempenho relacionado com a excentricidade mostrou um défice evidente e generalizado do centro para a periferia no grupo de hipertensos oculares, sugerindo uma perda progressiva de reserva funcional.

Palavras-chave: glaucoma, hipertensão ocular, progressão de doença, psicofísica, percepção de movimento, percepção de cor, sensibilidade ao contraste

Patterns of Impairment of Motion, Color and Achromatic Contrast Pathways in Distinct Stages of the Natural History of Glaucoma

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ABSTRACT

Purpose. To elucidate three important questions in the pathophysiology of glaucoma: (1) if patterns of damage evolve similarly in color, motion and achromatic pathways in the natural history of glaucoma; (2) if damage that occurs early in glaucoma is specific only to large ganglion cell pathways and (3) if eccentricity related patterns of damage exist across the natural history of the disease.

Methods. We studied a cohort of 41 participants divided across different groups (9 controls, 13 with ocular hypertension, 12 glaucoma suspects and 7 glaucoma patients) for correlation analysis of psychophysical damage with disease progression. We tested distinct visual pathways using three novel 2AFC (two-alternative forced choice) psychophysical tests that required the comparison and discrimination of a visual feature (motion, achromatic contrast and chromatic contrast across L, M and S cone contrast axes) between two separated moving single dots.

Results. All tests correlated with disease progression and could discriminate glaucoma subgroups even at an early disease stage (e.g. ocular hypertension *vs* controls). Eccentricity related patterns of damage were found, with a linear clear center *vs* periphery loss of performance being conspicuously observed in ocular hypertension.

Conclusions. We conclude that patterns of damage evolve similarly in color, motion and achromatic pathways in the natural history of glaucoma and that they are not specific to large ganglion cell pathways at early disease stages. Eccentricity related performance showed a striking and general center *vs* periphery decay pattern for ocular hypertension, suggesting a progressive loss of functional reserve.

Keywords: glaucoma, ocular hypertension, disease progression, psychophysics, motion perception, color perception, contrast sensitivity

INTRODUCTION

Glaucoma comprises a group of optic neuropathies related to the death or dysfunction of retinal ganglion cells (RGCs) leading to progressive visual loss. It was estimated that, in 2010, 60.5 million people had glaucoma, a figure which is expected to increase to 79.6 million in 2020.[1]

The diagnosis and evaluation of progression in glaucoma is based upon the identification of structural defects – caused by RGC death,[2,3] namely the thinning of the retinal nerve fiber layer and the cupping of the optic nerve head – and functional defects.[4–6] These functional defects range from *de facto* visual field loss, classically assessed by standard automated perimetry (SAP), to decreases on visual performance even at a pre-SAP loss stage.[7–9]

Such early functional defects depend on the relative degree of damage across the different central visual pathways for which two alternative hypotheses have been proposed. The preferential damage hypothesis states that glaucoma mainly targets large-fiber RGCs[10,11] which mainly belong to the magnocellular pathway.[7,12–14] However, there's now histological evidence of damage in all three major visual pathways[3] – magnocellular, parvocellular and koniocellular – as well as psychophysical evidence of early damage in red-green and blue-yellow channel processing, respectively related to the parvocellular and koniocellular pathways.[15–20] These findings support the reduced redundancy hypothesis which postulates that the increased sensitivity of certain tests is explained by the stimulation of specific and therefore sparse subsets of ganglion cells with a smaller functional reserve.[21–23]

This concept of functional reserve cannot be completely explained by either anatomic (e.g. dendritic field overlap) or physiological (e.g. receptive field overlap) terms alone[24,25] – such models must incorporate the notion of Ricco's law of spatial summation.[26] This law states that within the boundaries of Ricco's area (or perceptive field), the signal detection

threshold is inversely related to stimulus area (complete spatial summation). When the stimulus area exceeds Ricco's area, the relationship between area and threshold starts to obey Piper's law (partial spatial summation) until it operates through probability summation only. RGCs progressive dysfunction/death in glaucoma lead to an increase in Ricco's area,[24,27] meaning that with disease progression, a previously probability summated stimulus might now fall under the spatial summation rule, obeying Ricco's law and increasing the signal detection threshold.[28] Since Ricco's area naturally decreases from the central retina to the peripheral retina[29] (increased central redundancy), this might be the reason why glaucoma appears to preferentially target peripheral locations.[24]

Taking this into account, we created new psychophysical paradigms that try to functionally isolate specific ganglion cell populations with a relatively small degree of redundancy in order to attempt to relate glaucomatous neural losses with the natural history of the disease, from early to late stages. To this purpose we created discrimination tests that use small, moving and peripheral pairs of single dots which were targets for velocity, achromatic contrast and chromatic contrast discriminations.

With this, we aimed to evaluate the potential ability of these tests to probe disease progression. We also probed if these tests could detect of functional damage at an early disease stage (ocular hypertension). Finally, we explored the effect of eccentricity, namely if it was possible to relate disease progression with eccentricity related asymmetries.

METHODS

Patient Selection and Classification

Thirty-two patients recruited from glaucoma consultation of the University Hospital of Coimbra were included in the study and were compared with an age-matched group of controls (n = 9 eyes; mean age+SD = 64.570 ± 10.199 years).

The clinical study sample consists in 32 individuals in different stages of primary open angle glaucoma: ocular hypertension (HT; n = 13 eyes; mean age+SD = 65.143 ± 6.425 years; visual acuity (VA) = 0.83+0.16), glaucoma suspects (GS; n = 12 eyes; mean age+SD = 65.904 ± 11.163 years; VA = 0.82+0.16) and primary open angle glaucoma (G; n = 7 eyes; mean age+SD = 65.220 ± 10.622 years; VA = 0.86+0.15). ANOVA showed no significant age difference between groups. Patients with primary open angle glaucoma fulfilled the following criteria: cup-to-disc (C/D) vertical diameter of 0.5 or more, a mean deviation (MD) visual field global index less than -2 dB (or <5% of confidence interval). Glaucoma suspects had C/D of 0.5 or more and normal visual fields (MD more than -2 dB or >5%, of confidence interval). Patients with ocular hypertension were selected according to the following criteria: intraocular pressure (IOP) of 21 mmHg or more (on at least two occasions), MD more than -2 dB (or >5%, of confidence interval) and C/D less than 0.5.

All participants underwent a complete ophthalmic examination, including best corrected VA obtained with Snellen chart, Goldmann applanation tonometry (IOP measurement), slit lamp examination of the anterior segment, gonioscopy, retinal examination and optic disc evaluation. All individuals were also submitted to a perimetric examination (Standard Automated Perimetry, SAP) using the 30-2 standard program of Humphrey automated field analyzer (SITA-Fast strategy; HFA II, Carl Zeiss Meditec, Dublin, CA).

Exclusion criteria included the following: neuro-ophthalmologic diseases, retinal diseases, visual acuity less than 0.6, known color vision disorders, pseudophakic and aphakic

eyes, significant media opacities that preclude fundus examination and high ammetropy (sphere > + 4D; cylinder > + 2D).

Informed consent was obtained from all subjects, in strict accordance with the institutional guidelines and approval of our local ethics committee and after explanation of the objectives of the study. The research was conducted in accordance with the tenets of the Declaration of Helsinki.

Psychophysics

We programmed our experiments in MATLAB (MATLAB 2011a, The Mathworks Inc., Natick, MA, USA), using the Psychophysics Toolbox (PTB-3) extensions.[30–32] The experiments took place in a darkened room where subjects executed the experiments monocularly (only the dominant eye was tested), with refraction corrected for distance, 50 cm away from the display system. All stimuli were presented on a gamma-corrected 24" LCD-IPS monitor (ColorEdge CG243W, Eizo, Japan) with a resolution of 1920x1200 pixels and a refresh rate of 60 Hz. Spectral and luminance measurements were made using a spectroradiometer (PR-650 SpectraScan Colorimeter, Photo Research Inc., Chatsworth, PA, USA) from which 8-bit software look-up tables were built. These tables allowed us to display accurate stimuli with different luminance and chromaticity values on the LMS color space (transformed using human cone spectral sensitivities[33] at 10º).

We developed three novel 2AFC (two-alternative forced choice) psychophysical tests that required the comparison and discrimination of a visual feature (motion, achromatic contrast and chromatic contrast) between two separated moving single dots (a reference dot and a target dot). During 400 ms trials, the reference and target dots were simultaneously presented on randomly alternated visual hemi-fields, moving back and forth along a 2º pseudo-random linear trajectory (between 0º and 180º). After each trial, the subject gave a

verbal response (the instruction for each test is described below) which the experimenter stored by means of a standard keyboard (due to the subjects' average age and to avoid motor errors). There was no time limit for this response. The visual feature being evaluated was then adjusted in the following trial by using a logarithmic staircase procedure. The tests ended after 6 reversals and a discrimination threshold was calculated using the arithmetic mean of the last 4 reversals. Each test (including chromatic contrast sub-tests) was repeated four times, corresponding to one of four different meridian/eccentricity pairs (the horizontal meridian, 0º, was tested at 7.5º of eccentricity; the vertical meridian, 90º, at 10º; the oblique meridians, 45º and 135º, at 15º). Figure 1 contains a schematic illustration of the three tasks.

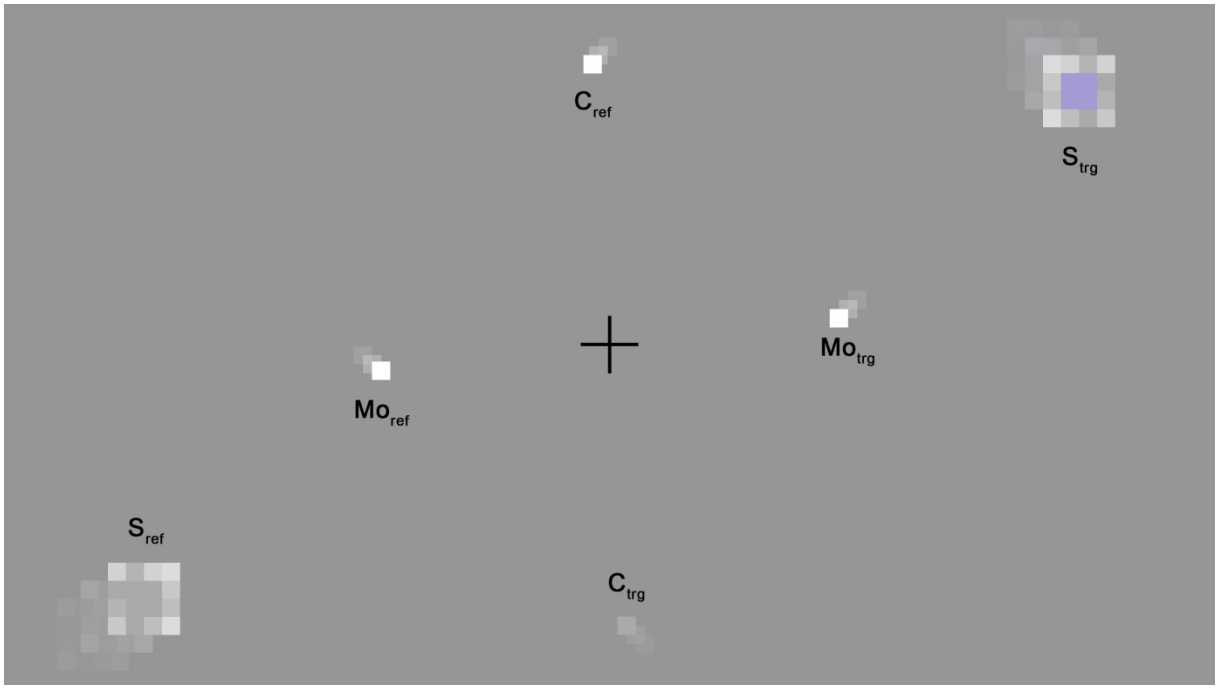

Figure 1. Schematic illustration of the **Mo**, motion, **C**, achromatic contrast and **S**, S-cone chromatic contrast tests, at the 0º, 90º and 45º meridians with an eccentricity of 7.5º, 10º and 15º, respectively. The tests consist on the comparison of moving dots, a reference dot (**ref**) and a target dot (**trg**), which differ on a specific visual attribute (in **Mo**, a speed difference between dots; in **C**, a luminance difference and in **S**, a chrominance, S-cone selective, difference).

We used two squared dots measuring 0.3ºx0.3º for the motion discrimination test and 0.6ºx0.6º for both achromatic and chromatic contrast discrimination tests. Fixation on a black central cross (size of 1º) was present during the whole test and monitored online used a camera. The background for all tests was a 25 cd/m^2 gray.

Motion discrimination test

In the motion discrimination test, the reference and target dots consisted of two white dots moving at different velocities. The reference dot velocity was always 5 deg/s (visual degrees per second), while the target dot velocity started at 24 deg/s and was then adjusted by the logarithmic staircase procedure (maximum step size of 1 dB and minimum of 0.05 dB). The subject was asked "Which dot is moving faster?" and answered either "Left/Right" (for the horizontal meridian) or "Up/Down" (for the vertical and oblique meridians).

Achromatic contrast discrimination test

In the achromatic contrast discrimination test, both reference and target dots moved at the same velocity (5 deg/s), but their luminance was distinct. The reference dot had a fixed luminance of 30 cd/m^2, while the target dot had a variable luminance that started at 80 cd/m^2 and was then adjusted by the logarithmic staircase procedure (maximum step size of 1 dB and minimum of 0.3 dB). The subject was asked "Which dot is brighter?" and answered either "Left/Right" (for the horizontal meridian) or "Up/Down" (for the vertical and oblique meridians).

Chromatic contrast discrimination test

The chromatic contrast discrimination test was composed of three sub-tests, in order to achieve preferential L, M and S-cone stimulation in isoluminance conditions (30 cd/m^2). In the S-cone sub-test, it was possible to obtain selective cone stimulation in isoluminance conditions, since the S-cone absorption spectrum has a very small overlap with the L and M-cone absorption spectra. In the L and M-cone sub-tests, since it is almost impossible to obtain selective cone stimulation in isoluminance conditions (due to the spectra overlap), we developed biased cone stimulation tests – the L-cone contrast exceeds the M-cone contrast in the L-cone sub-test and the reverse happens in M-cone sub-test (for instance, a variation of 15% in one cone produced a reciprocal variation of 2.5% in the other cone).

Both reference and target dots moved at the same velocity (5 deg/s) and had the same luminance (30 cd/m^2). Luminance cues were further avoided by a matrix of luminance noise around each dot. This matrix was composed of twelve 0.3º squared dots, with six luminance noise levels (30, 34, 38, 42, 46 or 48 cd/m^2), with two dots for each noise luminance value; the luminance of each dot randomly changed during the trial (synchronized to the screen refresh rate).

For all three tests, the reference dot was assigned the same relative coordinates (to the display's maximum white) in the LMS color space, lms(0.4106,0.4108,0.4241), giving it a gray, "colorless" appearance. The target dot starting point for the L, M, S-cone sub-tests was l(0.4732), m(0.5158), s(0.9), respectively. These appeared like a pale red, green and purple dot, respectively. Maximum and minimum step size in the staircase procedure for the L, M, S-cone sub-tests were 0.1 dB / 0.001 dB, 0.1 dB / 0.001 dB and 0.4 dB / 0.08 dB. The subject was asked "Which dot has color?" and answered either "Left/Right" (for the horizontal meridian) or "Up/Down" (for the vertical and oblique meridians).

Statistical Analysis

Statistical analysis was made with SPSS (IBM SPSS Statistics 21, IBM Corporation, NY, USA). Normality of the data across the study groups was verified using the Kolmogorov-Smirnov normality test. Since homogeneity of variance was sometimes violated in our study groups, we used the Welch F-Test for overall means comparison and the Games-Howell post-hoc test for multiple comparisons across groups. To study the effect of eccentricity in same task performance, we used repeated measures ANOVA, with both main effects and linear trends adjusted to the least significant difference (LSD).

RESULTS

Correlation with Disease Progression

We found that all of our new experimental measures strongly correlate with disease progression along our study groups. Using Spearman Rank Correlation, a significant correlation between each and every psychophysical threshold and ordered subject grouping categories was found (mean Rho ± SD = 0.66 ± 0.07; $p < 0.0001$ for all tests except achromatic contrast at the 0º meridian, with $p = 0.001$), revealing a distinct but progressive visual performance profiling through the disease's natural history. Figure 2, which shows percentile distributions of measured threshold and their progressive ranking across our study groups, exemplifies these results using one meridian as an example from each test.

Despite our relatively small sample size, our effect sizes were large enough to perform group mean comparisons using the Welch F-Test that revealed an overall significant difference between groups for every conducted test ($p < 0.0001$ for every test except achromatic contrast at the 0º meridian, with $p = 0.016$). We conducted a post-hoc analysis for pair-wise comparisons using the Games-Howell post-hoc test, which showed significant differences ($p < 0.05$) for all tests at every meridian between the control group and each patient group, except for four tests (achromatic contrast at the 0º meridian: only the control *vs* glaucoma suspect comparison was significant; achromatic contrast at the 45º meridian: only the control *vs* glaucoma comparison was significant; achromatic contrast at the 135º meridian: the control *vs* ocular hypertensive comparison was not significant; S-cone at the 0º meridian: the control *vs* glaucoma comparison was not significant). Overall, these results further reinforce the strength of our new paradigms to distinguish between control and patient groups. In particular the general differences between control and ocular hypertensive groups are noteworthy.

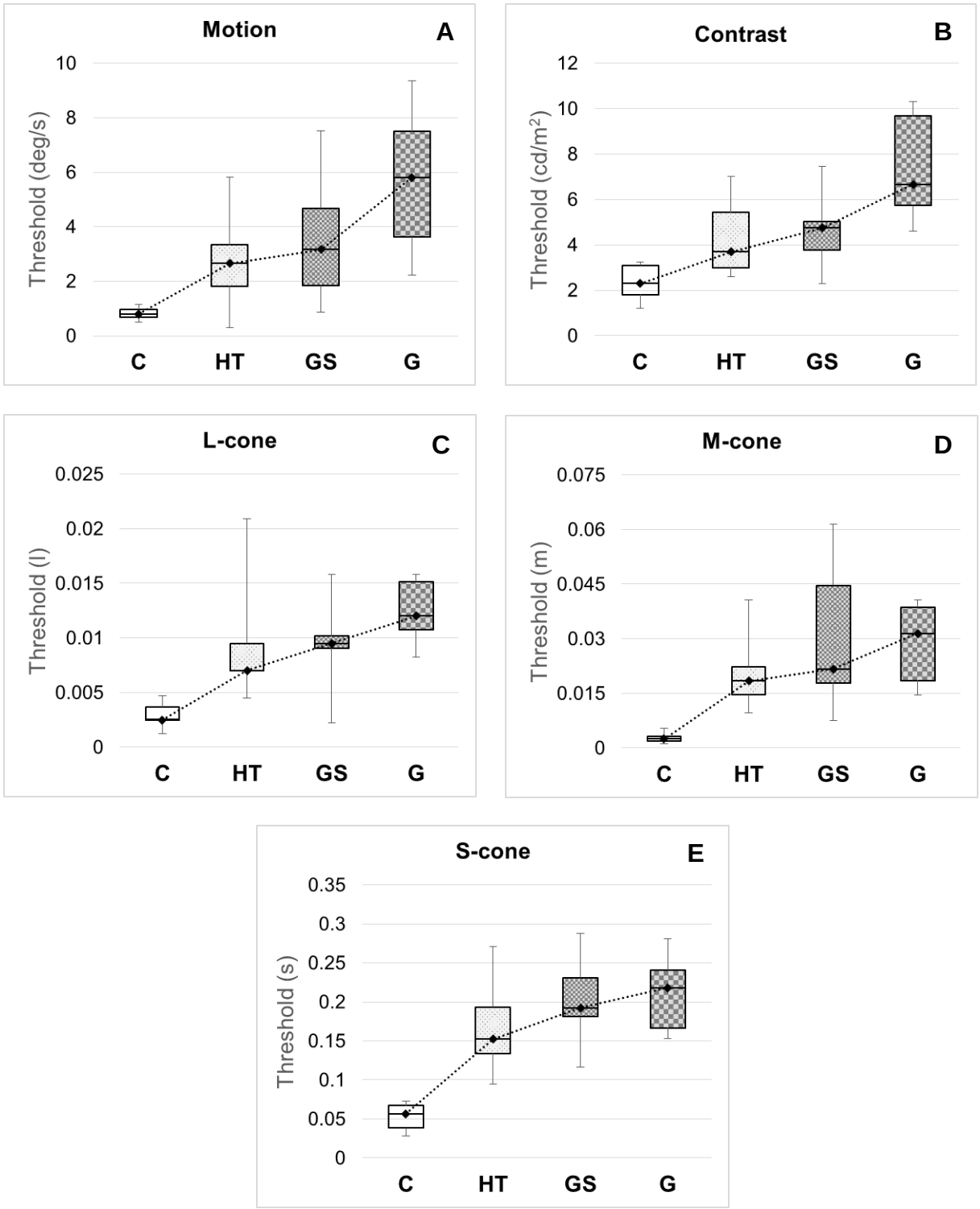

Figure 2. Representative examples of percentile box plots obtained for the study groups (**C**, control, **HT**, ocular hypertensive, **GS**, glaucoma suspect and **G**, glaucoma); only a meridian for each test is presented: **(A)** motion test at the 0º meridian, **(B)** achromatic contrast test at the 90º meridian, **(C)** L-cone test at the 135º meridian, **(D)** M-cone test at the 135º meridian and **(E)** S-cone test at the 45º

meridian. The bottom and top bars depict the 10th and 90th percentiles; the bottom and top borders of boxes represent the 25th and 75th percentiles; the line inside the boxes shows the median and the dotted line unites the median across study groups. The percentile box plots show a clear visual performance ranking along the disease progression stages, represented by each study group. All correlations in the presented tests between psychophysical thresholds and study groups were significant with $p < 0.0001$: **(A)** Rho=0.72, **(B)** Rho=0.68, **(C)** Rho=0.68, **(D)** Rho=0.66 and **(E)** Rho=0.71.

The Effect of Eccentricity in Task Performance

Building on the fact that we repeated each test at different eccentricities, we also studied the effect of eccentricity on task performance. To this purpose, we used Repeated Measures ANOVA to assess if there were group related asymmetries of visual performance with increasing eccentricity and whether these asymmetries varied in a linear way. We studied this effect on the control, ocular hypertensive and glaucoma study groups and thresholds obtained at the 45º and 135º meridians (same eccentricity) were averaged out. Group mean thresholds across eccentricities are plotted on Figure 3 and Figure 4.

First of all, there were no significant differences in task performance in the control group for every test (motion test – $p = 0.855$; achromatic contrast test – $p = 0.908$; L-cone test – $p = 0.499$; M-cone test – $p = 0.593$; S-cone test – $p = 0.134$). Clearly, subjects with normal visual function perform the same on our tests regardless of the eccentricity of the stimuli. Nonetheless, we observed a subtle, though not significant, increase in mean thresholds for the control group in the S-cone test, which could suggest differential eccentricity related performance within the physiological range.

Regarding the motion test, an interesting pattern was found. Ocular hypertensive subjects significantly vary visual performance with eccentricity ($p = 0.015$). Moreover, this variation occurs in a linear fashion ($p = 0.001$, partial eta-squared, $\eta_p^2 = 0.612$) meaning that

visual performance is progressively impaired from the center to the periphery. However, in glaucoma subjects there's a striking loss of significance in both mean differences (p = 0.241) and linear trend (p = 0.764). This pattern is also readily apparent in Figure 3.

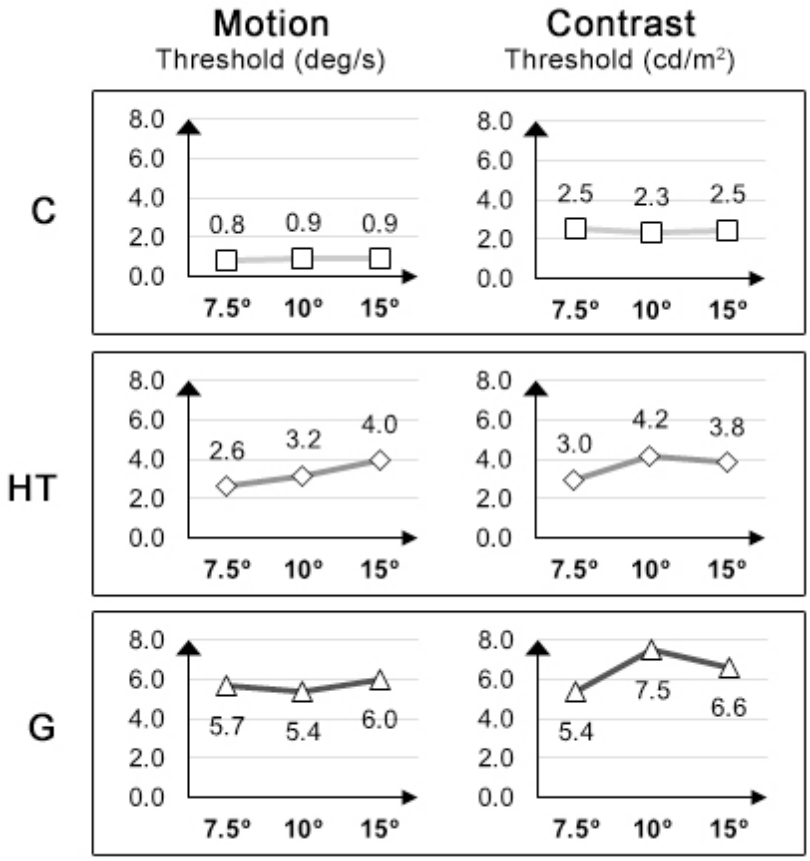

Figure 3. Group mean thresholds across eccentricities (**C**, control, **HT**, ocular hypertensive and **G**, glaucoma) for the motion and achromatic contrast test. A significant mean difference across eccentricities was only found in the ocular hypertensive group for both tests. A linear trend was found in both ocular hypertensive groups, clear and significant for the motion test and marginally significant in the achromatic contrast test, implying impaired visual performance from the center to the periphery.

In the achromatic contrast test (Figure 3), as in the motion test, a significant mean difference across eccentricities was only found in the ocular hypertensive group (p = 0.032), yet the linear trend was only marginally significant (p = 0.058, η_p^2 = 0.268).

Concerning the L-cone and M-cone tests (Figure 4), significant mean differences were found in both ocular hypertensive (p = 0.005 and p = 0.001, respectively) and glaucoma subjects (p = 0.011 and p = 0.023, respectively); the same was true for linear trends in both ocular hypertensive (p = 0.016, η_p^2 = 0.397 and p = 0.001, η_p^2 = 0.588, respectively) and glaucoma groups (p = 0.003, η_p^2 = 0.805 and p = 0.023, η_p^2 = 0.603, respectively).

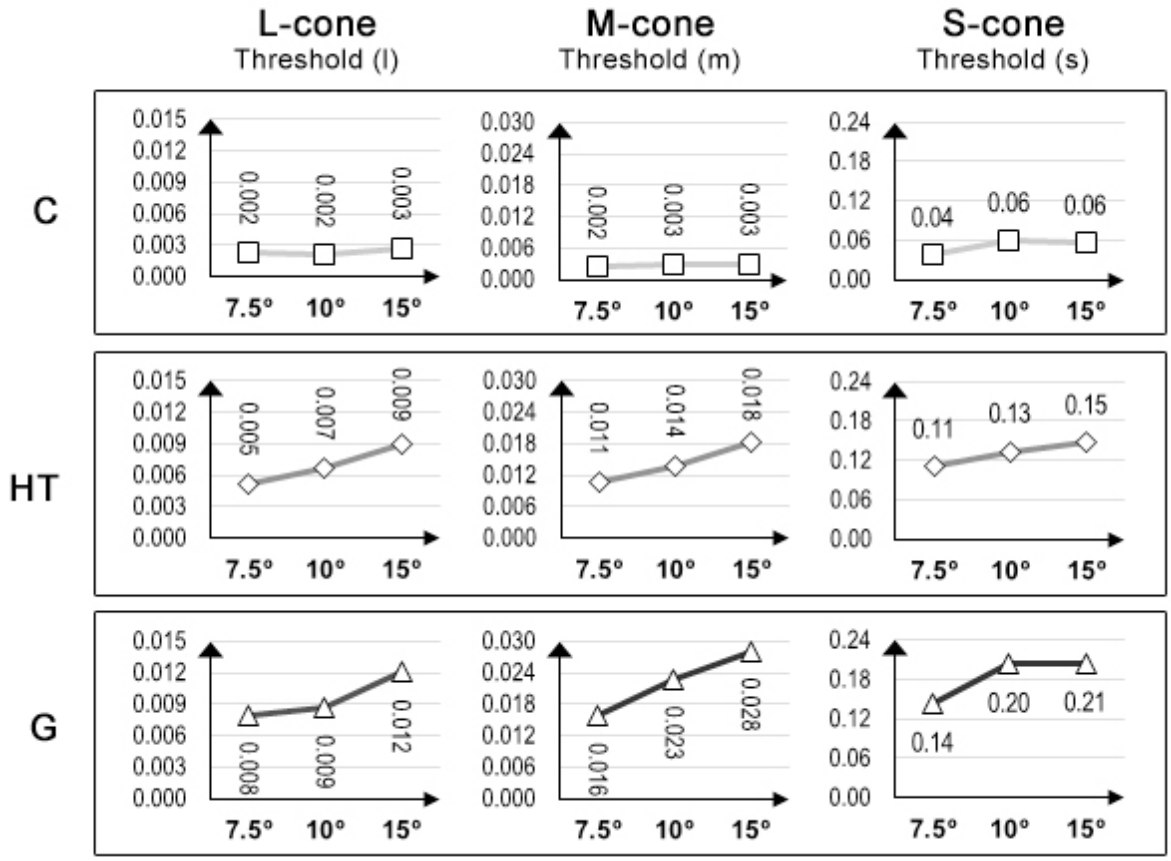

Figure 4. Group mean thresholds across eccentricities (**C**, control, **HT**, ocular hypertensive and **G**, glaucoma) for the L, M and S-cone tests. A significant mean difference and linear trend across eccentricities were found for both ocular hypertensive group and glaucoma in the L and M-cone tests and only for the ocular hypertensive group in the S-cone test.

Finally, the S-cone test (Figure 4) also reveals significant mean differences in the ocular hypertensive (p = 0.024) and glaucoma (p = 0.04) groups. However, a linear trend is only significant for the ocular hypertensive group (ocular hypertensive: p = 0.013, η_p^2 = 0.411; glaucoma: p = 0.082).

DISCUSSION

In this study we focused on the patterns of damage along the natural history of glaucoma in parallel visual pathways, as measured by LMS cone contrast thresholds, motion discrimination and achromatic contrast sensitivity. This enabled to test how disease pathways can be studied to test disease progression and if damage that occurs early in glaucoma is specific only to large ganglion cell pathways.

We found that patterns of damage progress along disease stages similarly in all motion, achromatic and chromatic pathways, therefore not specific to large ganglion cell pathways. Moreover, all tests discriminate glaucoma subgroups even for the early ocular hypertensive stage, which is in line with our hypothesis that a smaller degree of redundancy might allow a greater diagnostic accuracy.

The eccentricity related patterns of damage with linear center *vs* periphery decay were conspicuously observed in ocular hypertension and varied in a systematic manner across the natural history of the disease. This was particularly notorious in the motion, achromatic contrast and S-cone tests that revealed a clear loss of these trends in the glaucoma group. This finding is grounded in the hypothesis that with disease progression (namely from ocular hypertension to glaucoma) there's a loss of central redundancy, weaning out the eccentricity-related asymmetries that were found on the ocular hypertensive group. The model presented in Figure 5 prototypes the behavior found in the motion, achromatic contrast and S-cone test.

Meanwhile, on the L and M-cone tests, the linear trends found on the ocular hypertensive group were maintained in the glaucoma group. A possible explanation for these differences between the eccentricity related impairment patterns might be that with our tests we recruit different ganglion cells subsets from different visual pathways, therefore probing visual performance at varying degrees of redundancy.

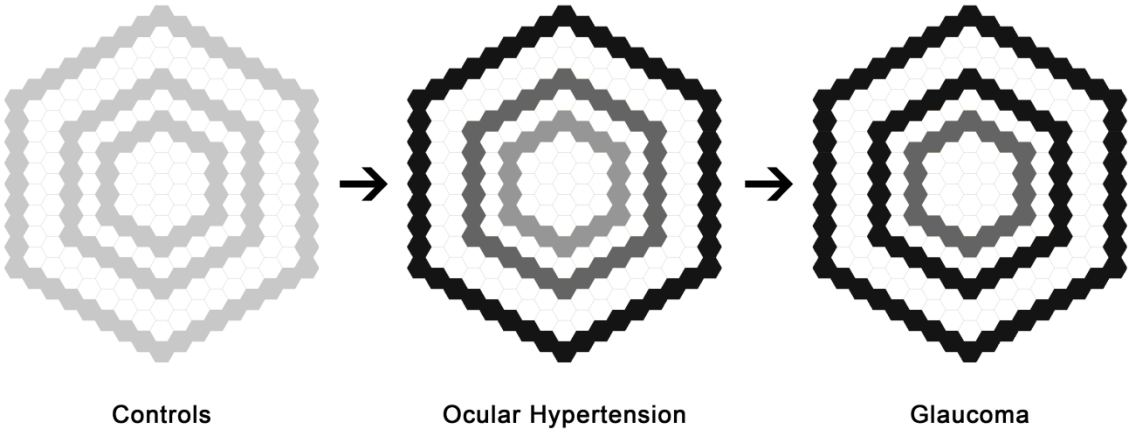

Figure 5. A theoretical model to explain visual performance asymmetries across disease stages. The inner ring represents 7.5º of eccentricity, the middle ring 10º and the outer ring 15º. With disease progression, visual performance is progressively impaired from the periphery (smaller redundancy) to the center (bigger redundancy), maximizing eccentricity related asymmetries in the ocular hypertension stage. In glaucoma, a loss of central redundancy weans out this asymmetry.

In sum, our work proves that disease mechanisms evolve similarly in color, motion and achromatic pathways in the natural history of glaucoma and that the bias for large ganglion cell pathways at early disease stages is much smaller than previously thought. Eccentricity related patterns of damage across the natural history of the disease and the clear periphery decay pattern for ocular hypertension suggests that progressive pattern of loss of functional reserve can be measured along the natural history of glaucoma.

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Anexo A

Normas editoriais para submissão de artigos para publicação na revista *Investigative Ophthalmology & Visual Science*.

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Articles present new data in one or more areas of vision research and are written concisely for a broad rather than a highly specialized audience. To be considered for publication, papers that are merely descriptions of new methods must be exceptional contributions, with implications extending beyond the particular applied area. Summaries of meetings/symposia, case reports, obituaries, and general review articles are not considered.

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