Visual Performance as a Function of Luminance in Glaucoma: The De Vries-Rose, Weber's, and Ferry-Porter's Law

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Purpose. To determine whether the De Vries-Rose, Weber's, and Ferry-Porter's law, which describe visual performance as a function of luminance, also hold in patients with glaucoma.

Methods. A case-control study with 19 glaucoma patients and 45 controls, all with normal visual acuity. We measured foveal and peripheral contrast sensitivity (CS) using static perimetry and foveal and peripheral critical fusion frequency (CFF; stimulus diameter 1°) as a function of luminance (0.02 to 200 cd/m^2). ANOVA was used to analyze the effect of glaucoma and luminance on CS and CFF; analyses were adjusted for age and sex.

Results. Foveally, logCS was proportional to log luminance at lower luminances (de Vries-Rose) and saturated at higher luminances (Weber); glaucoma patients had a 0.4 log unit lower logCS than controls ($P < 0.001$), independent of luminance. Peripherally, the difference was more pronounced at lower luminances ($P = 0.007$). CFF was linearly related to log luminance (Ferry-Porter). Glaucoma patients had a lower CFF compared with controls ($P < 0.001$), with a smaller slope of the CFF versus log luminance curve, for both the fovea (6.8 vs. 8.7 Hz/log unit; $P < 0.001$) and the periphery (2.5 vs. 3.4 Hz/log unit; $P = 0.012$).

Conclusions. Even in apparently intact areas of the visual field, visual performance is worse in glaucoma patients than in healthy subjects for a wide range of luminances, without a clear luminance dependency that is consistent across the various experiments. This indicates impaired signal processing downstream in the retina and beyond, rather than an impaired light adaptation in the strictest sense.

Keywords: perimetry, dark adaptation, flicker sensitivity, psychophysics, glaucoma

Glaucoma is a chronic and progressive eye disease characterized by loss of retinal ganglion cells and subsequent visual field loss. Traditionally, visual field loss in glaucoma has been described as asymptomatic peripheral visual field loss.[1] However, questionnaire studies revealed that glaucoma patients do report complaints; most frequently regarding visual performance under extreme (low, high, or changing) luminance conditions.[2–8] Complaints under extreme luminance conditions suggest impaired light adaptation, a mechanism whereby the visual system adapts itself to ambient luminance. Light adaptation starts in the photoreceptors,[9,10] but the circuitry beyond the receptors plays an important role as well.[11] The most logical location for light adaptation beyond the photoreceptors is the outer retina, a part of the retina that is not primarily affected in glaucoma. However, subtle changes in adaptation have been reported in glaucoma, which may be relevant to light adaptation.[12–15] Studying the luminance-specific visual performance of glaucoma patients could thus be important for a better understanding of the visual processing mechanisms affected by glaucoma, and may also be helpful for improving diagnostic tests or the assessment of, for example, driving performance. Recently, it has been shown that mesopic visual function was more strongly associated with nighttime driving performance than photopic visual function in healthy older adults,[16] and this difference might be even more pronounced in glaucoma patients. Thus far, studies that actually measured visual performance of glaucoma patients for a wide range of luminances seem lacking.

The following three major psychophysical laws are applicable to visual performance at different luminances: the De Vries-Rose law (contrast sensitivity [CS] is proportional to the square root of the background luminance at lower luminances),[17,18] Weber's law (CS is constant at higher luminances),[19] and Ferry-Porter's law (critical flicker frequency [CFF] is proportional to the logarithm of the background luminance).[20,21] Interestingly, these three laws were later shown to reflect the ability of a (healthy) visual system to adapt itself in such a way that the amount of visual information that can be processed is maximized—at each luminance level.[22,23] Thus far, the laws were only studied in healthy subjects. Evaluating them in glaucoma patients and relate the results to the theory of maximizing sensory information,[23] would allow us to determine which mechanisms are damaged, or changed, in glaucoma.

The aim of this study was to determine whether the De Vries-Rose, Weber's, and Ferry-Porter's law, which have been based on observations in healthy subjects, also hold in patients with glaucoma. For this purpose we determined the foveal and peripheral CS using static perimetry, and the foveal and peripheral CFF, for a wide range of luminances, in patients with glaucoma and healthy subjects.

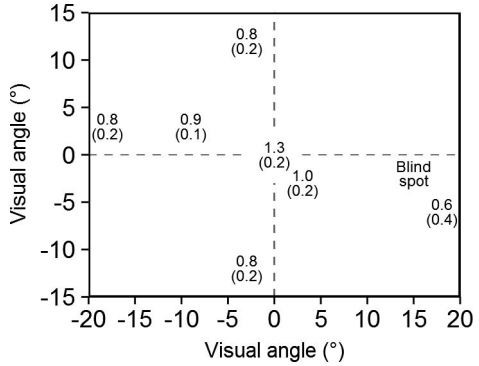

FIGURE 1. Static perimetry test location grid (in right eye format) with corresponding mean logCS as determined in our healthy subjects at 130 cd/m^2, with SD between brackets.

METHODS

Study Population

In this case-control study, we included 19 glaucoma patients (cases) and 45 healthy subjects (controls) for perimetry and CFF measurements. The ethics board of the University Medical Center Groningen (UMCG) approved the study protocol. All participants provided written informed consent. The study followed the tenets of the Declaration of Helsinki.

Glaucoma patients were selected from regular visitors of the outpatient department of the department of Ophthalmology, UMCG, using the visual field database of the Groningen Longitudinal Glaucoma Study; an observational cohort study in a clinical setting.[24] The study population for the current study consisted of POAG patients with a best-corrected visual acuity (BCVA) of 0.0 logMAR or better (up to 50 years of age) or 0.1 logMAR or better (above 50 years), in at least one eye. In case both eyes were eligible, the eye with the lower (more negative) standard automated perimetry mean deviation (MD) value was chosen.

Controls were recruited through advertising. We aimed for subjects between 40 and 70 years of age, approximately 15 subjects per decennium. Potential controls who responded to the advertisement filled out a questionnaire to screen for any known eye abnormality or a positive family history of glaucoma (exclusion criteria). After this preselection, an ophthalmic examination was performed, which included a BCVA measurement, a IOP measurement (TCT80; Topcon Medical Systems, Oakland, NJ, USA), a frequency doubling technology visual field test (FDT; C20-1 screening mode; Carl Zeiss, Jena, Germany), and a fundus examination with the Optos ultra-widefield retinal imaging device (200TX; Optos, Marlborough, MA, USA). Exclusion criteria were any known eye abnormality, a positive family history of glaucoma, a BCVA worse than 0.0 logMAR (up to 50 years of age) or 0.1 logMAR (above 50 years), an IOP above 21 mm Hg, any reproducibly abnormal test location at $P < 0.01$ on the FDT test result, a vertical cup-disc ratio above 0.7,[25] or any other fundus abnormality, as observed by an ophthalmologist (NJ) who evaluated the Optos images and all other available data. The BCVA was determined at 6 m at 100 cd/m^2, using different logMAR charts to avoid memorizing during refraction.[26] BCVA was defined as the last line of which at least three of five optotypes were named correctly. If both eyes were eligible, one eye was randomly chosen.

Data Collection

Perimetry and CFF measurements were performed after each other, at five different luminances. The experiments were preceded by a familiarization trial. Luminances were changed using (combinations of) neutral density (ND) filters (absorptive neutral density filters; #65-817, #65-820, #65-822; Edmund Optics, Barrington, NJ, USA) with optical density 0 (no filter), 1, 2, 3, and 4 (transmission 1, 0.1, 0.01, 0.001, and 0.0001). Luminance levels of the perimetry and CFF setup were measured with a Minolta luminance meter with built-in photometric filter (LS-110; Minolta Camera Co. Ltd., Osaka, Japan). Participants were pseudo-randomized in one of five different luminance sequences. After a change in luminance, we incorporated time to adapt to the new luminance at 2 minutes for every log unit decrease[27,28] and 1 minute per log unit increase in luminance (see Discussion section).[29,30] The experiments were performed monocularly and with optimal correction for the viewing distance (we excluded 1 patient from the perimetry analysis because of a wrong refractive correction during the experiment). No cycloplegia, mydriasis, or artificial pupil was used.

We did not dilate the pupil, as we were primarily interested in differences in overall visual function between glaucoma patients and healthy subjects. A compromised visual function might result from impaired pupil dilation at lower luminances, impaired pupil constriction at higher luminances, and/or changes in retinal signal processing. Our approach implies that retinal illuminance was not directly proportional to screen luminance and that the relationship between retinal illuminance and screen luminance might differ between the glaucoma patients and the controls. Retinal illuminance (Td) is the luminance of the screen (cd/m^2) multiplied by the pupil area (mm^2). We measured the pupil diameter at two luminances (2.36 and 236 cd/m^2) in order to be able to predict the pupil diameter at other luminances (see Data Analysis subsection). A circular stimulus with a diameter of 12° was projected on the monitor (see next paragraph) in darkness. The testing distance was 0.5 m and the subjects were instructed to fixate at the middle of the stimulus, with one eye occluded using an eye patch. After 2 minutes, a picture of the eye was taken using an infrared camera. Pupil size was calculated using the ratio between pupil and white-to-white distance (determined with a digital ruler from the infrared image), assuming a white-to-white distance of 12 mm.[31] We did not perform continuous measurements of the pupil diameter during the experiments, because the neutral density filters blocked the infrared radiation used by the device.

Static perimetry was performed using a high-luminance monitor (Radiforce G21; EIZO, Hakusan, Ishikawa, Japan) with a maximum luminance of 470 cd/m^2 and a size of 40° by 34° at the applied testing distance of 0.5 m, driven by the Psychophysics Toolbox (PTB-3)[32,33] with Octave (version 3.2.4; available in the public domain, www.gnu.org/software/octave/) for Linux (Ubuntu 10.10; Canonical, London, UK). A reduced testing grid was used, consisting of the fovea (coordinates [degree] in right-eye format [0,0]) and six peripheral test locations; three locations that are commonly affected ([−18,+3], [−9,+3], [−3,+12]) and three locations that are uncommonly affected ([+3,−3], [−3,−12], [+18,−6]) in early glaucoma.[34] The fixation target consisted of four thin lines with a length of 2°, starting at 1° from the center. The stimulus was a Goldmann size III increment, with a duration of 200 ms. During the test, the patient's head rested in a chin rest to maintain a testing distance of 0.5 m. A 4-2 dB staircase procedure (as was used in the original, classic central static threshold test)[35] was used to determine the threshold Weber contrast; CS was the inverse of this threshold. The mean background luminance of the monitor was 130 cd/m^2. Figure 1 shows the grid (in right eye format) and the mean logCS in each test location as determined in our healthy subjects, with SD between brackets. To avoid the inclusion of false-positive

Table. Characteristics of the Study Population

	Cases ($n = 19$)	Controls ($n = 45$)	*P* Value
Age (y; median [minimum, IQR, maximum])	71 (45, 64 to 73, 82)	54 (40, 47 to 65, 70)	<0.001
Sex, female, n (%)	6 (32)	23 (51)	0.25
Pupil diameter at 2.36 cd/m^2 (mm; median [IQR])	4.3 (3.0 to 4.7)	5.0 (4.4 to 5.7)	<0.001*
Pupil diameter at 236 cd/m^2 (mm; median [IQR])	3.2 (2.5 to 3.7)	3.2 (2.9 to 3.7)	0.23†
Visual acuity (logMAR; median [IQR])	0.00 (0.00 to 0.00)	0.00 (−0.08 to 0.00)	0.007‡
Median (IQR) HFA MD (dB)	−14.4 (−19.3 to −8.1)	NA	NA

NA, not applicable.
* Age-adjusted *P* value 0.017 (corresponding median 4.8 mm).
† Age-adjusted *P* value 0.34 (corresponding median 3.1 mm).
‡ Age-adjusted *P* value 0.45 (corresponding median 0.00).

measurements ('happy trigger'), the logCS corresponding to a specific data point was excluded if it was higher than the mean logCS plus 2.5 SD of the foveal test location of the controls (Chauvenet's criterion).[36] Output measures were (1) the logCS of the foveal test location, (2) the median logCS of the peripheral test locations that were not blind (i.e., the stimulus at that test location was detected at the highest 2 luminances), and (3) the logCS of the best-preserved peripheral test location in the glaucoma patients. For the third output measure, we first identified for each patient the peripheral test location with the smallest deviation from the controls at the highest two luminances and subsequently selected the test location that most frequently fulfilled this criterion within our group of glaucoma patients. We confined the corresponding analysis to the glaucoma patients for whom the selected test location was the best-preserved peripheral test location. If a stimulus was not detected at lower luminances, we defined the logCS of the concerning test location as –0.6 (corresponding to 2 dB above maximum contrast of the perimeter).

Foveal and peripheral CFF were determined using an astable multivibrator circuit attached to a green light-emitting diode (LED; LL-504PGC2V-G5-2CD; peak wavelength 525 nm; Luckylight, Shenzhen, China). The experimental setup consisted in total of two LEDs, one at the fovea (fixation), and one at 20° eccentricity at the horizontal meridian, nasally. The testing distance was 1.0 m. A diffusion filter was used to obtain stimuli with a diameter of 1° and a uniform luminance of 236 cd/m^2. The area surrounding the stimuli was dark. When the foveal CFF was determined, the nasal LED produced a continuous signal (i.e., did not flicker), and vice versa. The frequency of the flickering stimulus was increased by turning a rotary switch in preset steps of approximately 22% increase in frequency, going from 2 to 47 Hz in 16 steps. After each step, the subject was asked if the stimulus still appeared flickering, and if so, the frequency was increased again. When the stimulus was observed as steady, the frequency was decreased by turning the rotary switch half a step in the opposite direction, until flickering was again observed. The CFF was the mean of the frequency where subjects just saw a steady stimulus and the frequency where they again observed flickering. If the flickering stimulus was not detected at lower luminances, we defined the CFF as 1.75 Hz (corresponding to a 22% lower value than the minimum CFF we could detect).

Data Analysis

The study population was described using nonparametric descriptive statistics (median with interquartile range [IQR]). Univariable comparisons of continuous variables between cases and controls were made with a Mann-Whitney *U* test; proportions with a χ^2 test with Yates correction.

Glaucoma patients and controls appeared to differ regarding age. To enable a meaningful graphic representation of the data, we entered the controls with a weight factor. The weight factor was calculated, per 5-year bin, by dividing the number of glaucoma patients by the number of controls. The youngest bin included all subjects below age 50, the oldest bin all subjects over 65. We gave essentially a small weight to young controls. For example, the number of glaucoma patients and controls in the youngest bin was 2 and 15, respectively. The weight factor for this bin was 0.13 (2/15), resulting effectively in 2 controls. The age-weighted control group was only used in the graphs; all other analyses were adjusted by adding age as a covariate (see below).

To determine the influence of glaucoma and luminance on foveal and peripheral logCS and CFF, we performed complete case repeated measures ANOVA using aov in R (version 3.2.3; Foundation for Statistical Computing, Vienna, Austria). Age, sex, and the presence or absence of glaucoma were entered as between-subject variables, luminance as within-subject variable. In all models, we first corrected the data for age and sex and subsequently analyzed the effects of glaucoma and luminance and their interaction. A *P* value of 0.05 or less was considered statistically significant.

To determine the pupil diameter as a function of luminance from the pupil diameter measurements at 2.36 and 236 cd/m^2, we assumed a linear relationship between pupil diameter and log luminance in the applied luminance range, with censoring at a minimum diameter of 2 mm and a maximum diameter of 7 mm.[37] We adjusted the calculated pupil area for age and the Stiles-Crawford effect (1972),[38] assuming a Stiles-Crawford coefficient of 0.12.[39] The Stiles-Crawford effect is a directional sensitivity of the retina that reduces the effective pupil diameter for cones. This effect is not only present in the fovea, but also, and possibly even stronger, in the parafoveal/peripheral visual field.[40–42] We compared foveal and peripheral logCS and CFF as a function of luminance with those as a function of retinal illuminance.

Results

The Table shows the general characteristics of the study population. The mean age of the glaucoma patients and controls was 67.9 and 54.8 years, respectively ($P < 0.001$). After applying the age adjustment for the graphs (see Methods section), the mean age of the glaucoma patients and controls was 67.9 and 63.2 years, respectively ($P = 0.10$). Glaucoma patients and controls did not differ regarding sex. Most patients had moderate or severe glaucoma in the study eye, with a median (IQR) visual field MD of –14.4 (–19.3 to –8.1) dB.

Figure 2 presents the results for perimetry (CS measurements) as a function of luminance, for the foveal test location (Fig. 2A), the peripheral test locations that were not blind (Fig.

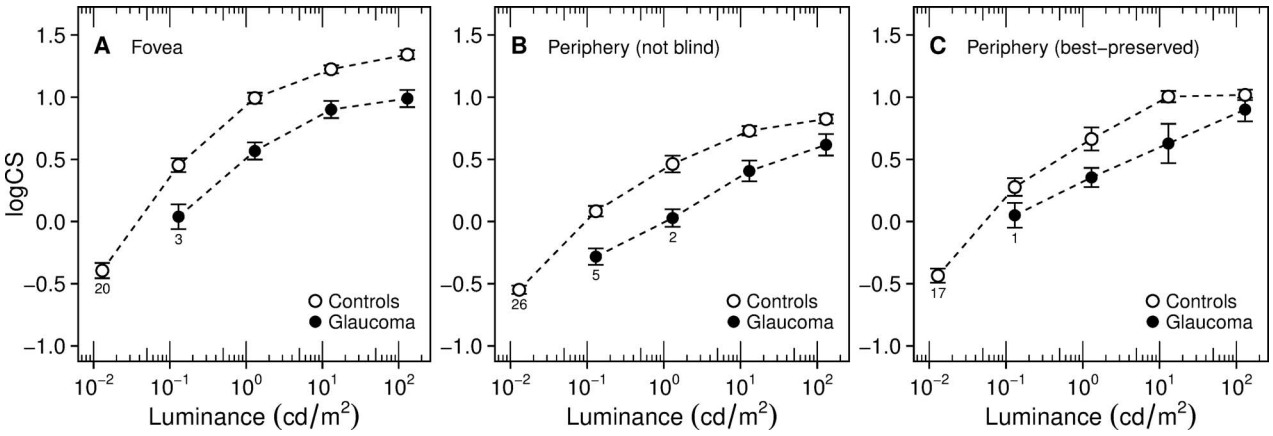

Figure 2. Perimetry as a function of luminance for glaucoma patients (*filled circles*) and controls (*open circles*). (**A**) Central contrast sensitivity; (**B**) contrast sensitivity of the nonblind parts of the peripheral visual field; and (**C**) contrast sensitivity of the best-preserved part of the peripheral visual field (test location [+3,–3]). *Error bars*: ±1 standard error. If applicable, individual data points were marked with the number of subjects who were not able to see the stimulus. Not seen was replaced by –0.6 (see Methods section). Data points for which the stimulus was not seen by more than 50% of the subjects were omitted.

2B), and for the best-preserved peripheral test location in the glaucoma patients (Fig. 2C). This best-preserved peripheral test location was (+3,–3) in all but six glaucoma patients; these six patients were excluded from Figure 2C and the corresponding analysis (see below). At the lowest luminance, none but one glaucoma patient could see the central stimulus, and none but two glaucoma patients could see any peripheral stimulus, compared with approximately half of the controls. To maintain a sufficiently large number of complete cases for the ANOVA, we performed the ANOVA without the lowest luminance. LogCS was significantly influenced by luminance for both the glaucoma patients and the controls ($P < 0.001$). Glaucoma patients had a lower logCS in the fovea, in the nonblind peripheral visual field, and in the best-preserved peripheral test location (all $P < 0.001$), compared with the controls. The difference between glaucoma patients and controls was approximately 0.4 log units in the fovea, independent of luminance (no significant interaction between glaucoma and luminance; $P = 0.06$). However, in the nonblind peripheral visual field and the best-preserved peripheral test location, the difference between glaucoma patients and controls was more pronounced at lower luminances (significant interaction between glaucoma and luminance; $P = 0.007$ for the nonblind peripheral visual field; $P = 0.008$ for the best-preserved peripheral test location). Between 0.13 and 1.3 cd/m^2, the slope of the foveal logCS as a function of log luminance curve was 0.53 for the glaucoma patients and 0.54 for the controls, which is close to the slope of 0.5 as predicted by the De Vries-Rose law. At higher luminances, the CS started to saturate, which is in agreement with Weber's law. In the same luminance range (0.13–1.3 cd/m^2), the slope of the curve of the nonblind peripheral visual field was 0.31 for the glaucoma patients and 0.38 for the controls. For the best-preserved peripheral test location, the slope was 0.30 for the glaucoma patients and 0.39 for the controls. At higher luminances, the peripheral CS started to saturate for the controls, but (within our luminance range) not for the glaucoma patients. Below 0.13 cd/m^2, the slope appeared to be steeper than 0.5 for the controls, especially in the fovea. As mentioned above, most of the glaucoma patients were unable to see the stimulus below this luminance.

Figure 3 presents the foveal (Fig. 3A) and peripheral (Fig. 3B) CFF as a function of luminance. One glaucoma patient was not able to provide consistent answers to define the CFF and was therefore excluded. Two glaucoma patients did not observe any flickering in the periphery and were excluded for the corresponding analysis. CFF was significantly influenced by luminance for both the glaucoma patients and the controls ($P < 0.001$). For both the glaucoma patients and the controls in the central and peripheral visual field, there was an essentially linear relationship between CFF and log luminance (in agreement with Ferry-Porter's law); the explained variance by a linear fit was 0.98 and 0.98 for the central visual field and 0.99 and 0.95 for the peripheral visual field, for the glaucoma patients and controls, respectively. Glaucoma patients had a lower CFF compared with controls, for both the fovea ($P < 0.001$) and the periphery ($P < 0.001$). The slope of the foveal CFF versus log luminance curve of the patients (6.8 [95% confidence interval 6.2–7.4] Hz per log unit) was smaller than the slope of the controls (8.7 [8.0–9.4]), resulting in a more pronounced CFF difference toward higher luminances ($P < 0.001$). A similar difference was found for the peripheral CFF (slope 2.5 [1.9–3.1] and 3.4 [2.6–4.1] Hz per log unit in patients and controls, respectively; $P = 0.012$).

The curves depicting the foveal and peripheral logCS and CFF as a function of retinal illuminance belonging to the glaucoma patients and the controls (figures not shown) were very similar to the corresponding curves as a function of luminance (Figs. 2 and 3), regarding their shape and spacing. This indicates that the small differences in pupil diameter between the glaucoma patients and controls were unlikely to influence our findings.

Discussion

In the central visual field, the De Vries-Rose and Weber's law hold in both healthy subjects and patients with glaucoma; the logCS versus log background luminance curve of glaucoma patients is shifted downward compared with the curve of the healthy subjects. In the peripheral visual field, there is a less clear transition between the De Vries-Rose and Weber's law in glaucoma patients and, related to that, the difference in logCS between the glaucoma patients and controls becomes less pronounced at high luminance. Ferry-Porter's law holds in the central and peripheral visual field of both healthy subjects and patients with glaucoma. The slope of the CFF as function of log background luminance curves is smaller in glaucoma patients than in healthy subjects.

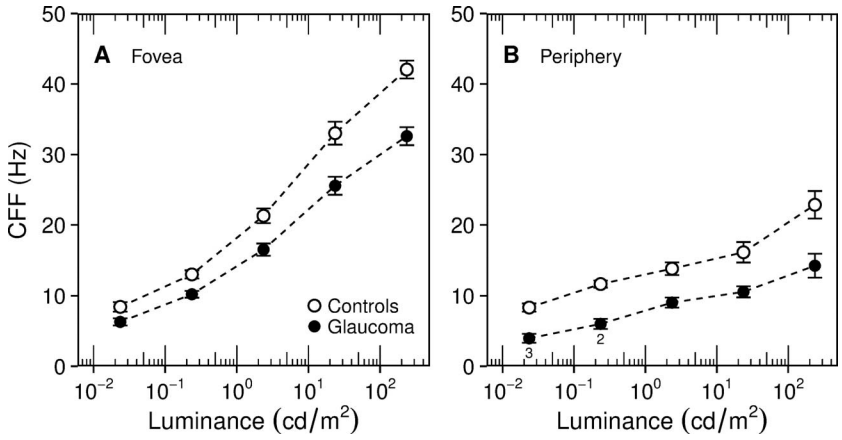

FIGURE 3. Critical flicker frequency as a function of luminance for glaucoma patients (*filled circles*) and controls (*open circles*). (**A**) Central CFF and (**B**) peripheral CFF at 20° nasally. *Error bars*: ±1 standard error. If applicable, individual data points were marked with the number of subjects who were not able to see the stimulus. Not seen was replaced by 1.75 Hz (see Methods section).

The static perimetry results of our study can be compared with four earlier studies in healthy subjects and one study including glaucoma patients. Our main contribution is a much wider luminance range. Aulhorn and Harms[43] studied the influence of luminance on static perimetry in 10 healthy subjects. They found a small decrease in retinal sensitivity going from 100 to 10 apostilb (asb), and a profound decrease going from 10 to 1 asb, which is in agreement with our results (3.14 asb = 1 cd/m^2). Three other studies focused on static perimetry at different luminances in healthy subjects.[44–46] These studies used neutral density filters of maximal 3.0 log units to attenuate the default background luminance of 1.3 (Octopus) and 10 (Humphrey Field Analyzer) cd/m^2. They all found a decrease in retinal sensitivity already at 1.0 log unit attenuation, which is in agreement with our results. We found only one study that performed static perimetry at different luminances and included patients with glaucoma.[47] In that study, the authors measured retinal sensitivities using Goldmann size III stimuli in 18 glaucoma patients and 10 controls, at two different background luminances (3.15 and 31.5 asb, that is, 1 and 10 cd/m^2). Up to an eccentricity of 15°, the difference in perimetric sensitivity between 3.15 and 31.5 asb was identical for glaucoma patients and controls, which is in agreement with our results (Fig. 2).

The CFF results of our study can be compared with earlier studies in healthy subjects that measured the CFF at different luminances, and studies in glaucoma patients that measured the CFF at a single luminance. Our main contribution is the luminance dependency of CFF in glaucoma. Studies that measured CFF for small central stimuli in healthy subjects found slopes of approximately 10 Hz per log unit, which is close to our result in the controls (8.6 [7.9–9.4]).[48–51] We found a lower slope in the periphery than centrally, which is in agreement with two studies that included the same eccentricity and a similar stimulus size.[52,53] One study found that the slope did not depend on eccentricity,[51] which might be explained by the size of the illuminated background (whole retina for Lythgoe and Tansley,[51] 10° for Hecht and Verrijp,[52] and no illuminated background for Brooke[53] and our study). Several studies focused on CFF in glaucoma, under one luminance condition. Three early studies found that almost all included glaucoma patients had a CFF outside the CFF range of the controls, in both the fovea and periphery.[54–56] More recent studies on flicker perimetry found areas under the receiver operating curve of 0.8 and higher for the discrimination between glaucoma patients and healthy subjects; they did not report the CFF per eccentricity.[57–59] The study of Essock[60] seems to be an exception, with a similar CFF for early glaucoma patients and controls, using a 5° stimulus at 120 cd/m^2 background luminance.

In this study, there was a difference in age distribution between glaucoma patients and controls. Because psychophysics is quite exhausting and concentration was necessary during all tests, we aimed to include participants not exceeding 70 years of age. This was an inclusion criterion for the controls, but, because glaucoma is a disease of the elderly, the vast majority of patients with glaucoma within our database was above 60 years of age. This resulted in a different age distribution between the groups. Still, the groups showed sufficient overlap to disentangle the effects of age and glaucoma with multivariable analysis, and all statistical analyses and graphs were adjusted for age. With these measures, we aimed to minimize the influence of the different age distributions on our findings as much as possible.

After each change in luminance, we incorporated time to adapt to the new luminance. This time, 2 minutes of adaptation per log unit decrease in luminance and 1 minute per log unit increase, was a trade off between the wish to keep the total duration of the experiment acceptable for the subjects and the aim to reach a new steady state. Hecht et al.[27] showed that, when going from a luminance of 300 mL (955 cd/m^2; 6092 Td at 2.85-mm pupil diameter) to darkness, a constant cone threshold for a small central stimulus was reached after approximately 2 minutes. Mote and Riopelle[28] studied the time course of foveal dark adaptation, for a series of preexposure luminances and durations. For 5 minutes preexposure to 565 mL (1798 cd/m^2; 5650 Td at 2 mm pupil diameter), a steady state was reached after approximately 2 minutes.[28] The highest retinal illuminance used in our study was approximately 1900 Td (236 cd/m^2 at 3.2-mm pupil diameter). Hence, our 2 minutes of adaptation per log unit decrease in luminance should be sufficient to reach adapted cone function (the fovea does not contain rods). We recently confirmed this for a 5-log unit luminance step in healthy subjects and glaucoma patients.[30] Adaptation to an increase in luminance is much faster,[29,30] and therefore we chose 1 minute of adaptation per log unit increase in luminance. Regarding the peripheral visual field, rods take much longer to adapt after a luminance decrease than cones and therefore we presume that we measured primarily cone function in the peripheral visual field as well. On the other hand, the observed slopes in the peripheral visual field were slightly smaller than 0.5, suggesting

some rod activity.[61] The relative contribution of rods and cones depends on many factors, and cannot easily be determined in the mesopic range.[62] In any case, because the adaptation durations were the same in the glaucoma patients and controls, the CS measurements offer a fair comparison between both groups.

In the perimetry experiment, we used a reduced testing grid in order to be able to perform a series of tests within a limited amount of time. As we originally aimed to study the role of luminance as a function of damage, we employed both test locations that are commonly affected and test locations that are uncommonly affected in early glaucoma.[34] However, it turned out that, in damaged areas, the sensitivity was often unrecordable as soon as the luminance was reduced. For that reason, we focused on the apparently intact areas. Because test locations with higher eccentricities had—on average—more glaucomatous damage, the exclusion of damaged parts resulted in a slightly smaller median eccentricity of the included peripheral test locations in the glaucoma patients than in the controls (9° vs. 12°). Therefore, the reported difference between both groups in the peripheral visual field (Fig. 2B and corresponding analysis) might be an underestimation. However, the effect of a 3° difference in median eccentricity on logCS is small (Fig. 1). Interestingly, we found that even the best-preserved part of the visual field (test location [+3,−3]) showed an impaired sensitivity at all but the highest luminance included (Fig. 2C and corresponding analysis).

A simple model of early vision (visual information processing in the eye and the visual pathways up to roughly the striate cortex) may consist of (1) retinal units (photoreceptors and spatiotemporal filters including interactions between adjacent units; light adaptation is presumed to be located in these units),[11] (2) noisy channels with limited bandwidth (retinal ganglion cells/optic nerve),[22,23] and (3) pooling of adjacent channel outputs at the level of the cortex (a step that has been shown to be essential for understanding the variability in static perimetry and the relationship between perimetric and structural measures of glaucomatous damage).[63–65] For the foveal increment, the logCS versus log luminance curve showed a vertical shift (Fig. 2A), that is, the difference in logCS between the glaucoma patients and controls was independent of luminance. In terms of the abovementioned model, this implies intact (that is, no impaired light adaptation) retinal units of which the number may be decreased and or the connectivity to the brain lost (as opposed to a horizontal shift, which would point to damaged retinal units).[66] For the peripheral increment, we observed a similar vertical shift at all but the highest luminance included (130 cd/m^2; Figs. 2B and 2C). This suggests that the effect of an impaired connectivity depends on luminance in the periphery but not in the fovea, or also in the fovea but only at a much higher luminance.[30] Spatial summation has been shown to depend on eccentricity[67–69] and luminance,[70] and to differ between glaucoma patients and controls, at least at the default luminance used in perimetry.[47,71,72] At this default luminance and within 15° eccentricity, the area of complete spatial summation (Ricco's area) is smaller than Goldmann size III in healthy eyes but not always in eyes with glaucoma.[71] This implies a difference in redundancy between healthy and glaucoma. A decrease of this difference at the highest luminance could explain the observed deviation from a purely vertical shift.

For CFF, an impaired connectivity would result in a CFF versus log luminance relationship with similar slope but lower ordinate for glaucoma patients versus controls.[22] This is globally what we observed. However, in our data the difference in CFF seems to increase with increasing luminance, suggesting a delayed or incomplete decrease in temporal summation with increasing luminance. An increase in temporal pooling has been described in glaucoma at the default luminance used in perimetry.[73]

In conclusion, even in apparently intact areas of the visual field, visual performance is worse in glaucoma patients than in healthy subjects for a wide range of luminances, without a clear luminance dependency that is consistent across the various experiments. This indicates impaired signal processing downstream in the retina and beyond, rather than an impaired light adaptation in the strictest sense. Nevertheless, as visual performance drops down in everyone when going from twilight to moonlight, glaucoma patients will cross a certain minimum contrast sensitivity needed for reasonable vision earlier than healthy subjects. This may explain the higher frequency of visual complaints in glaucoma patients at low luminances, and agrees with questionnaire studies addressing this topic.[2,3,5,6,8] These studies also revealed complaints in situations with a high luminance and with a sudden change in luminance. Hence, future research could focus on luminances beyond the highest luminance of the current study and on the dynamic properties of light and dark adaptation in glaucoma.

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References

1. Duke-Elder S, Jay B. Simple glaucoma. In: Duke-Elder S, ed. *System of Ophthalmology*. Vol. XI. St. Louis: CV Mosby; 1969: 443–477.
2. Lee BL, Gutierrez P, Gordon M, et al. The Glaucoma Symptom Scale. A brief index of glaucoma-specific symptoms. *Arch Ophthalmol*. 1998;116:861–866.
3. Janz NK, Wren PA, Lichter PR, Musch DC, Gillespie BW, Guire KE. Quality of life in newly diagnosed glaucoma patients: the collaborative initial glaucoma treatment study. *Ophthalmology*. 2001;108:887–898.
4. Janz NK, Wren PA, Lichter PR, et al. The Collaborative Initial Glaucoma Treatment Study: interim quality of life findings after initial medical or surgical treatment of glaucoma. *Ophthalmology*. 2001;108:1954–1965.
5. Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. *Br J Ophthalmol*. 1999;83:546–552.
6. Hu CX, Zangalli C, Hsieh M, et al. What do patients with glaucoma see? Visual symptoms reported by patients with glaucoma. *Am J Med Sci*. 2014;348:403–409.
7. Tatemichi M, Nakano T, Hayashi T, et al. Symptoms related to glaucomatous visual field abnormalities among male Japanese workers in a population-based setting. *Acta Ophthalmol*. 2010;90:546–551.
8. Bierings RAJM, van Sonderen FLP, Jansonius NM. Visual complaints of patients with glaucoma and controls under optimal and extreme luminance conditions. *Acta Ophthalmol*. 2018;96:288–294.
9. Boynton RM, Whitten DN. Visual adaptation in monkey cones: recordings of late receptor potentials. *Science*. 1970; 170:1423–1426.
10. Valeton JM, van Norren D. Light adaptation of primate cones: an analysis based on extracellular data. *Vision Res*. 1983;23: 1539–1547.

11. Hood DC. Lower-level visual processing and models of light adaptation. *Annu Rev Psychol*. 1998;49:503–535.
12. McKendrick AM, Badcock DR, Morgan WH. Psychophysical measurement of neural adaptation abnormalities in magnocellular and parvocellular pathways in glaucoma. *Invest Ophthalmol Vis Sci*. 2004;45:1846–1853.
13. Sun H, Swanson WH, Arvidson B, Dul MW. Assessment of contrast gain signature in inferred magnocellular and parvocellular pathways in patients with glaucoma. *Vision Res*. 2008;48:2633–2641.
14. Dul M, Ennis R, Radner S, Lee B, Zaidi Q. Retinal adaptation abnormalities in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2015;56:1329–1334.
15. Junoy Montolio FG, Meems W, Janssens MSA, Stam L, Jansonius NM. Lateral inhibition in the human visual system in patients with glaucoma and healthy subjects: a case-control study. *PLoS One*. 2016;11:e0151006.
16. Kimlin JA, Black AA, Wood JM. Nighttime driving in older adults: effects of glare and association with mesopic visual function. *Invest Ophthalmol Vis Sci*. 2017;58:2796–2803.
17. Rose A. The sensitivity performance of the human eye on an absolute scale. *J Opt Soc Am*. 1948;38:196–208.
18. de Vries HL. The quantum character of light and its bearing upon threshold of vision: the differential sensitivity and visual acuity of the eye. *Physica*. 1943;10:553–564.
19. Duke-Elder S, Weale RA. The sensation of light. In: Duke-Elder S, ed. *System of Ophthalmology*. Vol. IV. St. Louis: CV Mosby; 1968:583.
20. Ferry ES. Persistence of vision. *Am J Sci*. 1892;44:192–207.
21. Porter TC. Contributions to the study of flicker. Paper II. *Proc R Soc Lond*. 1902;70:313–329.
22. van Hateren JH. Spatiotemporal contrast sensitivity of early vision. *Vision Res*. 1993;33:257–267.
23. van Hateren JH. Theoretical predictions of spatiotemporal receptive fields of fly LMCs, and experimental validation. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol*. 1992;171:157–170.
24. Heeg GP, Blanksma LJ, Hardus PLLJ, Jansonius NM. The Groningen Longitudinal Glaucoma Study. I. Baseline sensitivity and specificity of the frequency doubling perimeter and the GDx nerve fibre analyser. *Acta Ophthalmol Scand*. 2005;83:46–52.
25. Wolfs RC, Borger PH, Ramrattan RS, et al. Changing views on open-angle glaucoma: definitions and prevalences–The Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2000;41:3309–3321.
26. Jansonius NM, Kooijman AC. The effect of defocus on edge contrast sensitivity. *Ophthalmic Physiol Opt*. 1997;17:128–132.
27. Hecht S, Haig C, Wald G. The dark adaptation of retinal fields of different size and location. *J Gen Physiol*. 1935;19:321–337.
28. Mote FA, Riopelle AJ. The effect of varying the intensity and the duration of preexposure upon foveal dark adaptation in the human eye. *J Gen Physiol*. 1951;34:657–674.
29. Hood DC, Finkelstein MA. Sensitivity to light. In: Boff K, Kaufman L, Thomas J, eds. *Handbook of Perception and Human Performance*. Vol. I. New York, NY: John Wiley and Sons; 1986:5.3–5.66.
30. Bierings RAJM, Kuiper M, van Berkel CM, Overkempe T, Jansonius NM. Foveal light and dark adaptation in patients with glaucoma and healthy subjects: a case-control study. *PLoS One*. 2018;13:e0193663.
31. Rüfer F, Schröder A, Erb C. White-to-white corneal diameter: normal values in healthy humans obtained with the Orbscan II topography system. *Cornea*. 2005;24:259–261.
32. Brainard DH. The psychophysics toolbox. *Spat Vis*. 1997;10:433–436.
33. Pelli DG. The VideoToolbox software for visual psychophysics: transforming numbers into movies. *Spat Vis*. 1997;10:437–442.
34. Junoy Montolio FG, Wesselink C, Jansonius NM. Persistence, spatial distribution and implications for progression detection of blind parts of the visual field in glaucoma: a clinical cohort study. *PLoS One*. 2012;7:e41211.
35. Anderson DR, Patella VM. *Automated Static Perimetry*. St. Louis: Mosby; 1999.
36. Chauvenet W. *A Manual of Spherical and Practical Astronomy*. 5th ed. Vol. 2. Philadelphia, PA: J.B. Lippincott Company; 1906:469–566.
37. Watson AB, Yellott JI. A unified formula for light-adapted pupil size. *J Vis*. 2012;12(10):12.
38. Crawford BH. The Stiles-Crawford effects and their significance in vision. In: Jameson D, Hurvich LM, eds. *Handbook of Sensory Physiology*. Vol VII/4. Berlin, Germany: Springer; 1972:470–483.
39. Atchison DA, Smith G. Light level at the retina. In: *Optics of the Human Eye*. Edinburgh, UK: Butterworth-Heinemann; 2002:125.
40. Westheimer G. Dependence of the magnitude of the Stiles-Crawford effect on retinal location. *J Physiol*. 1967;192:309–315.
41. Enoch JM, Hope GM. Directional sensitivity of the foveal and parafoveal retina. *Invest Ophthalmol*. 1973;12:497–503.
42. De Lint PJ, Berendschot TT, van Norren D. Local photoreceptor alignment measured with a scanning laser ophthalmoscope. *Vision Res*. 1997;37:243–248.
43. Aulhorn E, Harms H. Visual perimetry. In: Jameson D, Hurvich LM, eds. *Handbook of Sensory Physiology*. Vol VII/4. Berlin, Germany: Springer; 1972:102–145.
44. Klewin KM, Radius RL. Background illumination and automated perimetry. *Arch Ophthalmol*. 1986;104:395–397.
45. Heuer DK, Anderson DR, Feuer WJ, Gressel MG. The influence of decreased retinal illumination on automated perimetric threshold measurements. *Am J Ophthalmol*. 1989;108:643–650.
46. Membrey L, Kogure S, Fitzke FW. A comparison of the effects of neutral density filters and diffusing filters on motion perimetry, white on white perimetry and frequency doubling perimetry. In: Wall M, Wild JM, eds. *Perimetry Update 1998/1999*. The Hague, Germany: Kugler Publications; 1999:75–83.
47. Fellman RL, Lynn JR, Starita RJ, Swanson WH. Clinical importance of spatial summation in glaucoma. In: Heijl A, ed. *Perimetry Update 1988/1989*. Amsterdam, the Netherlands: Kugler and Gedini; 1989:313–324.
48. Pokorny J, Smith VC. Luminosity and CFF in deuteranopes and protanopes. *J Opt Soc Am*. 1972;62:111–117.
49. Tyler CW, Hamer RD. Analysis of visual modulation sensitivity. IV. Validity of the Ferry-Porter law. *J Opt Soc Am A*. 1990;7:743–758.
50. Hamer RD, Tyler CW. Analysis of visual modulation sensitivity. V. Faster visual response for G- than for R-cone pathway? *J Opt Soc Am A*. 1992;9:1889–1904.
51. Lythgoe RJ, Tansley K. The relation of the critical frequency of flicker to the adaptation of the eye. *Proc Biol Sci*. 1929;105:60–92.
52. Hecht S, Verrijp CD. Intermittent stimulation by light: III. The relation between intensity and critical fusion frequency for different retinal locations. *J Gen Physiol*. 1933;17:251–268.
53. Brooke RT. The variation of critical fusion frequency with brightness of various retinal locations. *J Opt Soc Am*. 1951;41:1010–1022.
54. Miles P. Flicker fusion fields; III. Findings in early glaucoma. *Arch Ophthal*. 1950;43:661–677.

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55. Tyler CW. Specific deficits of flicker sensitivity in glaucoma and ocular hypertension. *Invest Ophthalmol Vis Sci*. 1981;20:204–212.
56. Campbell CJ, Rittler MC. The diagnostic value of flicker perimetry in chronic simple glaucoma. *Trans Am Acad Ophthalmol Otolaryngol*. 1959;63:89–98.
57. Yoshiyama KK, Johnson CA. Which method of flicker perimetry is most effective for detection of glaucomatous visual field loss? *Invest Ophthalmol Vis Sci*. 1997;38:2270–2277.
58. Matsumoto C, Takada S, Okuyama S, Arimura E, Hashimoto S, Shimomura Y. Automated flicker perimetry in glaucoma using Octopus 311: a comparative study with the Humphrey Matrix. *Acta Ophthalmol Scand*. 2006;84:210–215.
59. Nomoto H, Matsumoto C, Takada S, et al. Detectability of glaucomatous changes using SAP, FDT, flicker perimetry, and OCT. *J Glaucoma*. 2009;18:165–171.
60. Essock EA, Fechtner RD, Zimmerman TJ, Krebs WK, Nussdorf JD. Binocular function in early glaucoma. *J Glaucoma*. 1996;5:395–405.
61. Steinhardt J. Intensity discrimination in the human eye: I. The relation of delta I/I to intensity. *J Gen Physiol*. 1936;20:185–209.
62. Stockman A, Sharpe LT. Into the twilight zone: the complexities of mesopic vision and luminous efficiency. *Ophthalmic Physiol Opt*. 2006;26:225–239.
63. Swanson WH, Felius J, Pan F. Perimetric defects and ganglion cell damage: interpreting linear relations using a two-stage neural model. *Invest Ophthalmol Vis Sci*. 2004;45:466–472.
64. Gardiner SK, Swanson WH, Demirel S, McKendrick AM, Turpin A, Johnson CA. A two-stage neural spiking model of visual contrast detection in perimetry. *Vision Res*. 2008;48:1859–1869.
65. Bijl P. *Aspects of Visual Contrast Perception* [doctorate thesis]. Utrecht, the Netherlands: University of Utrecht; 1991.
66. Seiple WH, Holopigian K, Greenstein VC, Hood DC. Sites of cone system sensitivity loss in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 1993;34:2638–2645.
67. Scholtes AM, Bouman MA. Psychophysical experiments on spatial summation at threshold level of the human peripheral retina. *Vision Res*. 1977;17:867–873.
68. Volbrecht VJ, Shrago EE, Schefrin BE, Werner JS. Spatial summation in human cone mechanisms from 0 degrees to 20 degrees in the superior retina. *J Opt Soc Am A Opt Image Sci Vis*. 2000;17:641–650.
69. Wilson ME. Invariant features of spatial summation with changing locus in the visual field. *J Physiol*. 1970;207:611–622.
70. Barlow HB. Temporal and spatial summation in human vision at different background intensities. *J Physiol*. 1958;141:337–350.
71. Redmond T, Garway-Heath DF, Zlatkova MB, Anderson RS. Sensitivity loss in early glaucoma can be mapped to an enlargement of the area of complete spatial summation. *Invest Ophthalmol Vis Sci*. 2010;51:6540–6548.
72. Felius J, Swanson WH, Fellman RL, Lynn JR, Starita RJ. Spatial summation for selected ganglion cell mosaics in patients with glaucoma. In: Wall M, Heijl A, eds. *Perimetry Update 1996/1997 Proceedings of the XIIth International Perimetric Society Meeting*. Amsterdam, the Netherlands: Kugler; 1997:213–221.
73. Mulholland PJ, Redmond T, Garway-Heath DF, Zlatkova MB, Anderson RS. Spatiotemporal summation of perimetric stimuli in early glaucoma. *Invest Ophthalmol Vis Sci*. 2015;56:6473–6482.

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