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Spatial contrast sensitivity from star- to sunlight in healthy subjects and patients with glaucoma

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ABSTRACT

Glaucoma is traditionally considered an asymptomatic disease until later stages. However, questionnaire studies revealed visual complaints related to various tasks, especially under extreme luminance conditions (such as outdoor at night on an unlit road or outside in the sun). We measured contrast sensitivity (CS) over a luminance range of 6 log units spanning the scotopic to photopic range and we aimed (1) to determine whether Weber's law also holds under extremely high luminance conditions and (2) to compare CS as a function of spatial frequency and luminance between glaucoma patients and healthy subjects. We included 22 glaucoma patients and 51 controls, all with normal visual acuity. For the second aim, we used a subgroup of 22 age-similar controls. Vertically oriented sine-wave gratings were generated with a projector-based setup (stimulus size 8x5 degrees). CS was measured monocularly at 1, 3, and 10 cycles per degree (cpd); mean luminance ranged from 0.0085 to 8500 cd/m^2. ANOVA was used to analyze the effect of glaucoma, luminance, and spatial frequency on logCS. In controls, Weber's law held for 3 and 10 cpd; for 1 cpd, CS dropped above 1000 cd/m^2 ($P = 0.003$). The logCS versus log luminance curves did not differ grossly between patients and controls ($P = 0.14$; typically 0–0.2 log units); the difference became larger with decreasing luminance ($P = 0.003$) but did not depend clearly on spatial frequency ($P = 0.27$). We conclude that differences between glaucoma and healthy were relatively modest for the spatially redundant, static stimulus as used in the current study.

1. Introduction

Glaucoma is a chronic and progressive eye disease characterized by loss of retinal ganglion cells (RGCs) and subsequent loss of visual function. Traditionally, the loss of visual function has been described as asymptomatic, at least in early glaucoma (Duke-Elder, 1969). However, asymptomatic seems to be the case only at an appropriate luminance; visual complaints are frequently reported for extreme (low, high, or changing) luminance conditions (Bierings, van Sonderen, & Jansonius, 2018; Hu et al., 2014; Janz et al., 2001; Janz et al., 2001; Lee et al., 1998; Nelson, Aspinall, & O'Brien, 1999; Tatemichi et al., 2010). 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 (Boynton & Whitten, 1970; Valeton & van Norren, 1983), but the retinal neurons beyond the receptors plays an important role as well (Aguilar & Stiles, 1954; Baylor, Nunn, & Schnapf, 1984; Hood, 1998; Schnapf, Nunn, Meister, & Baylor, 1990). 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, earlier studies using the Tübingen perimeter found that the difference in sensitivity between glaucoma patients and controls was higher in the scotopic than in the photopic condition (Drum, Armaly, & Huppert, 1986; Glovinsky, Quigley, Drum, Bissett, & Jampel, 1992), and the scotopic condition seemed to uncover abnormalities in ocular hypertensives as well (Goldthwaite, Lakowski, & Drance, 1976; Stirling, Pawson, Brimlow, & Vernon, 1996). We found recently, over a wide luminance range, that the difference in perimetric sensitivity between glaucoma patients and controls was independent of luminance in the fovea but more pronounced at lower luminances in the peripheral visual field (Bierings, de Boer, & Jansonius, 2018). Also, glaucoma patients did not have different adaptation times compared to controls for foveal vision (Bierings, Overkempe, van Berkel, Kuiper, & Jansonius, 2018; Jonas, Zäch, & Naumann, 1990). Importantly, the luminance outdoor at noon on a sunny day (typically 10,000 cd/m^2) is approximately 1000 times higher than the luminance used during perimetry. Studies that actually measured visual performance under high luminance conditions are scarce, and in glaucoma patients apparently completely lacking. This is possibly related to the fact that default clinical tests do not surpass 10 (perimetry) or typically 100 (visual

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acuity, contrast sensitivity [CS]) cd/m^2, and makes a thorough study of visual performance at high luminance overdue.

Two major psychophysical laws describe visual performance at different luminances: the De Vries-Rose law (CS is proportional to the square root of the background luminance at low luminances; de Vries, 1943; Rose, 1948), and Weber's law (CS is constant at high luminances; Duke-Elder, 1968). The De Vries-Rose law is attributed to the Poisson statistics of photon capture; it implies that, in the corresponding luminance range, the quantum efficiency of the retina is constant (de Vries, 1956). The transition to Weber's law corresponds to the decrease in quantum efficiency needed to keep up with higher luminances (de Vries, 1956); especially at the highest luminances, bleaching plays a role here (Valeton & van Norren, 1983). The De Vries-Rose and Weber's law can be understood from the point of view of photoreceptor physiology, but also from the point of view of information processing. Interestingly, the laws were 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 (van Hateren, 1992, 1993). The resulting theory of maximizing sensory information predicts that the visual system performs spatial low-pass filtering at low luminances and spatial band-pass filtering at high luminances (van Hateren, 1992). This implies that the relationship between CS and background luminance depends on the spatial frequency of the stimulus. Indeed, the contrast sensitivity function (CSF; CS as a function of spatial frequency) has been shown to differ between low and intermediate luminance (Coletta & Sharma, 1995; Comerford, Thorn, & Corwin, 1987; Daitch & Green, 1969; De Valois, Morgan, & Ma Snodderly, 1974; Hess & Howell, 1988; Hess, 1990; Mustonen, Rovamo, & Näsänen, 1993; Peli, Arend, & Labianca, 1996; Rovamo, Mustonen, & Näsänen, 1994, 1995; van Meeteren & Vos, 1972). Only one study, with only one subject, extended the measurements towards the higher luminances (Van Nes & Bouman, 1967). To reproduce their findings and extend the luminance range, we addressed the CSF towards high luminances as the first issue in this study.

Several studies compared the CSF between glaucoma patients and healthy subjects, in one luminance condition. The majority reported a difference between glaucoma patients and controls in the whole spatial frequency range (Adams, Heron, & Husted, 1987; Ansari, Morgan, & Snowden, 2002; Arden & Jacobson, 1978; Horn, Martus, & Korth, 1995; Onal, Yenice, Cakir, & Temel, 2008; Ross, Bron, & Clarke, 1984; Vaegan & Halliday, 1982), or only for higher spatial frequencies (Korth, Horn, Storck, & Jonas, 1989; Sample, Juang, & Weinreb, 1991; Vaegan & Halliday, 1982; Wood & Lovie-Kitchin, 1992). Others reported a normal CS in glaucoma patients (Drance et al., 1987; Korth et al., 1989; Lundh, 1985a, 1985b; Sokol, Domar, & Moskowitz, 1980; Sponsel et al., 1991). We did not find any study that compared the CSF between glaucoma patients and healthy controls as a function of luminance. This is the second issue we addressed in this study.

The aims of this study were (1) to determine whether Weber's law also holds under extremely high luminance conditions and how this depends on spatial frequency, and (2) to compare CS as a function of spatial frequency and luminance between glaucoma patients and healthy subjects. For this purpose we measured the CS for a low, intermediate, and high spatial frequency (1, 3, and 10 cycles per degree [cpd]) in a group of healthy subjects and patients with glaucoma, for a luminance range of 6 log units spanning the scotopic to photopic range (10^{-2}–10^4cd/m^2).

2. Methods

2.1. Study population

We included 22 glaucoma patients (cases) and 51 healthy subjects (controls) in this cross-sectional case-control study. 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 department of Ophthalmology, UMCG, using the visual field database of the Groningen Longitudinal Glaucoma Study (Heeg, Blanksma, Hardus, & Jansonius, 2005). The inclusion criteria were the presence of primary open angle glaucoma and 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. If both eyes were eligible, the eye with the lower (more negative) standard automated perimetry mean deviation (MD) value was chosen.

Healthy subjects were recruited by advertisement (posters with a call for participation as healthy volunteer in eye research were placed in public buildings in the city of Groningen). We aimed for subjects between 40 and 75 years of age, approximately 15 subjects per decennium. Potential healthy subjects were screened for any known eye abnormality or a positive family history of glaucoma (exclusion criteria). After this preselection, an ophthalmic examination was performed, including a BCVA measurement, a non-contact intraocular pressure (IOP) measurement (TCT80; Topcon Medical Systems, Oakland, 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, 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 mmHg, any reproducibly abnormal test location at $P < 0.01$ on the FDT test result, a vertical cup-disc ratio above 0.7 (Wolfs et al., 2000), or any other fundus abnormality, as observed by an ophthalmologist [NJ] who evaluated the Optos images and all other available data. If both eyes were eligible, one eye was randomly chosen.

2.2. Data collection

A projector (P1387W; Acer) was positioned at the rear of a see-through PVC projection screen. The resulting screen width and height were 28 and 18 cm, respectively, and the maximal luminance of the screen 16,000 cd/m^2. The surrounding area (width 90 cm, height 70 cm) was retro-illuminated by LED construction lights, yielding a white surrounding area with a luminance that was approximately 50% of the mean screen luminance during the experiments. The projector beam and surrounding area illumination were separated by black cardboard sheets to prevent crosstalk of light. The testing distance was 2 m, resulting in a stimulus size of 8 by 5 degrees (± 4 degrees horizontally and ± 2.5 degrees vertically) and a surrounding area of 25 by 20 degrees. Luminances were measured with a Minolta luminance meter with built-in photometric filter (LS-110; Minolta Camera Co. Ltd., Japan).

Contrast sensitivity was measured using vertically oriented sine-wave gratings, with three spatial frequencies: 1, 3, and 10 cpd. The psychophysical method was a tracking method according to von Békésy (Jansonius & Kooijman, 1997; Von Békésy, 1967). Contrast was defined as Michelson contrast ($[L_{max}\text{-}L_{min}]/[L_{max} + L_{min}]$, where L_{max} and L_{min} are the maximum and minimum luminance on the screen, respectively). At the beginning of each experiment, the contrast was negligible (0.00001) and gradually increased. When the subject observed the sine-wave grating, a button was pressed and held. As a result, the contrast gradually decreased until the grating was not observed anymore, and the button was released. Contrast then increased again, and the procedure was repeated to obtain a total of twelve reversals (taking together about 1 min). The speed of the contrast change was 0.3 log per second. To increase accuracy, the first two reversals, and the maximum and minimum of the upper and lower reversals were excluded. The log of the contrast threshold was then calculated as the mean of the log of the remaining six reversals, i.e., three upper and three lower reversals. This methods gives thresholds quite similar to those obtained with a

two-alternative forced choice method and is, because of its symmetry around the threshold, insensitive to differences in speed of contrast change and reaction time (Nio et al., 2005). The CS is the reciprocal of the contrast threshold, that is, logCS = −log(contrast threshold). If the variability in the reversals exceeded the 97.5th percentile of the variability in the healthy subjects, the observation was excluded from the analysis (this concerned 2.3% of the thresholds in the healthy subjects and 1.2% in the glaucoma patients). By definition, offering a Michelson contrast of more than 1 is not possible. If one or more of the remaining three upper reversals had a value that saturated at 1, or if the subject was not able to see the stimulus at all, the contrast threshold could not be calculated and the corresponding logCS was set at 0 (CS = 1). Spatial frequency/luminance combinations for which this was the case in more than 50% of the controls were excluded.

Contrast sensitivity measurements were performed under seven different luminance conditions. The mean background luminance of the experimental setup was 8500 cd/m^2. Luminance conditions were changed using (combinations of) neutral density (ND) filters (absorptive neutral density filters; #65-817, #65-820, #65-822; Edmund Optics) with optical density 0 (no filter), 1, 2, 3, 4, 5, and 6 (transmission 1, 0.1, 0.01, 0.001, 0.0001, 0.00001, and 0.000001). Controls were pseudo-randomized in one of two different luminance sequences, e.g., dark-to-light or light-to-dark. After a change in luminance, we incorporated time to adapt to the new luminance: two minutes for every log unit decrease; one minute per log unit increase in luminance (Bierings et al., 2018). Glaucoma patients repeated the test in the other sequence on a separate day; half of the patients had the dark-to-light sequence on the first day, the other half started with the light-to-dark sequence. The results did not differ for the two luminance sequences. Therefore, the results of both sequences were averaged. The experiments were performed monocularly (see Section 2.1 for selection of the study eye) and with optimal correction for the viewing distance. No cycloplegia, mydriasis, or artificial pupil was used. Measurements were preceded by a familiarization trial.

Before the CS measurements, we measured the pupil diameter at two different luminances (1 and 450 cd/m^2). For these measurements, we used a circular stimulus with a diameter of 12° in darkness. The subjects were instructed to fixate at the middle of the stimulus, with one eye occluded. After two minutes of adaptation, a picture of the eye was taken with an eye-tracker. Pupil size was calculated using the ratio between pupil and white-to-white distance, assuming a white-to-white distance of 12 mm (Rüfer, Schröder, & Erb, 2005). From the pupil diameter at these two luminances, we calculated the pupil diameter at other luminances (see Section 2.3).

2.3. Data analysis

For description of the study population, we used nonparametric descriptive statistics (median with interquartile range [IQR]). For univariable comparisons between cases and controls, we used a Mann-Whitney test for continuous variables and a Chi-square test with Yates correction for proportions.

To see whether Weber's law also holds under high luminance conditions and how this depends on spatial frequency (first aim of this study), we plotted the logCS of the healthy subjects as a function of log background luminance, for each spatial frequency tested. We verified the De Vries-Rose law by determining the slope of a line through the two lowest data points and we determined the transition luminance (luminance at which the De Vries-Rose law transitions into Weber's law) from the intersection of a line through the two lowest data points and a horizontal line determined by the two highest data points. To compare CS as a function of spatial frequency and luminance between glaucoma patients and controls (second aim of this study), we plotted the logCS of both groups as a function of log background luminance, per spatial frequency. Differences between curves were analyzed with ANOVA (see below).

The glaucoma patients were older than the healthy subjects. For the analyses concerning only the healthy subjects (first aim), we used all 51 healthy subjects. For the analyses where we compared glaucoma and healthy (second aim), we used data from the oldest 22 healthy subjects (1:1 ratio glaucoma versus healthy), yielding an age-similar control group.

To incorporate the influence of the pupil area on the luminance, we also presented the logCS as a function of retinal illuminance in Troland (screen luminance in cd/m^2 multiplied by pupil area in mm^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 (Watson & Yellott, 2012). We adjusted the calculated pupil area for the Stiles-Crawford effect (Baron & Enoch, 1982; Crawford, 1972), assuming a Stiles-Crawford coefficient of 0.12 (Atchison & Smith, 2002). The Stiles-Crawford effect is a directional sensitivity of the retina that reduces the effective pupil diameter for cones (see Section 4 for a discussion regarding the relative contribution of cones and rods in our experiments).

To determine the influence of glaucoma, luminance, and spatial frequency on the logCS, we performed a repeated measures ANOVA using aov in R (version 3.2.3; Foundation for Statistical Computing, Vienna, Austria). Because ANOVA requires complete cases, we only included luminance values for which all spatial frequencies could be observed (that is, 0.85 cd/m^2 and above; for criteria see Section 2.2); any missing observations (1.3%) for the included luminance values were imputed using missForest in R. The presence or absence of glaucoma was entered as between-subject variable; luminance and spatial frequency as within-subject variables. A P value of 0.05 or less was considered statistically significant.

3. Results

Table 1 shows the general characteristics of the study population, including the healthy subjects, the subset of age-similar controls, and the glaucoma patients. Most patients had moderate to severe glaucoma in the study eye, with a median (IQR) visual field MD of −13.5 (−16.8 to −10.5) dB. All but two patients had a normal or near normal (that is, P > 0.05) foveal sensitivity on their most recent standard automated

Table 1
Characteristics of study population.

	Healthy subjects (n = 51)	Age-similar controls (n = 22*)	Glaucoma patients (n = 22)	P value†
Age (year; median [IQR])	58 (49–66)	66 (64–70)	68 (60–73)	0.93
Gender, female, n (%)	27 (53%)	11 (50%)	8 (36%)	0.54
Pupil diameter at 1 cd/m^2 (mm; median [IQR])	5.3 (4.7–5.8)	4.9 (4.3–5.7)	4.3 (3.4–5.1)	0.04
Pupil diameter at 450 cd/m^2 (mm; median [IQR])	3.0 (2.7–3.4)	3.0 (2.6–3.4)	3.1 (2.5–3.4)	0.80
Visual acuity (logMAR; median [IQR])	−0.08 (−0.08–0.00)	−0.04 (−0.08–0.00)	0.00 (−0.08–0.00)	0.15
HFA MD (dB; median [IQR])	NA	NA	−13.5 (−16.8–−10.5)	NA

IQR = interquartile range; MD = mean deviation; NA = not applicable.
* Subset containing the 22 oldest healthy subjects (see Section 2).
† P value cases versus age-similar controls.

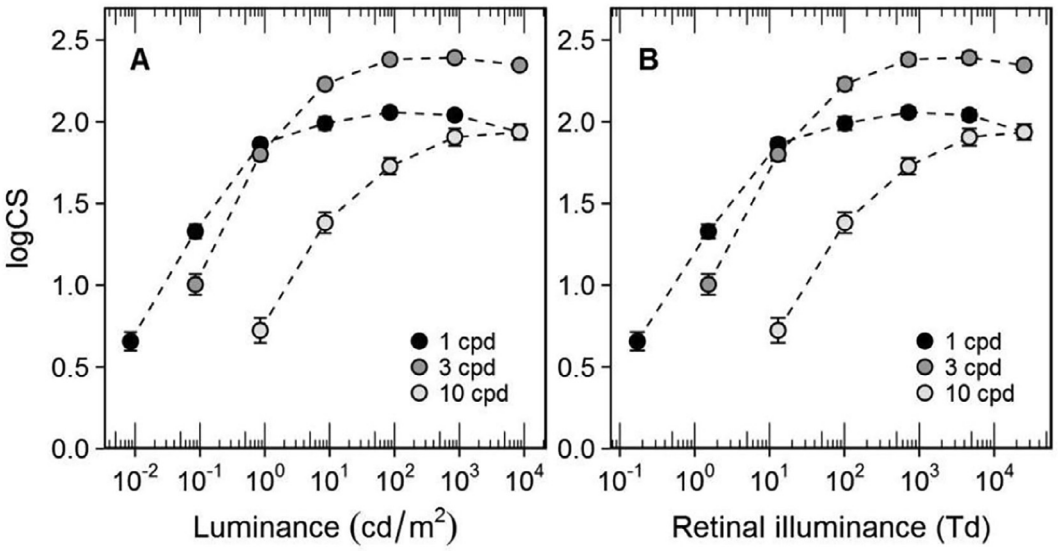

Fig. 1. Spatial contrast sensitivity as a function of luminance (A) and retinal illuminance (B) of controls. Error bars (often smaller than the data points itself) denote ± 1 standard error. LogCS decreased significantly at the highest luminance for 1 cpd (P = 0.003). The corresponding pupil diameters were 2.0, 2.8, 3.6, 4.5, 5.4, 6.2, and 7.0 mm.

perimetry visual field test (the foveal test location is the only test location of the 30–2 grid that is located within our contrast sensitivity stimulus area).

Fig. 1 presents the CS as a function of luminance (Fig. 1A), and retinal illuminance (Fig. 1B), for the healthy subjects. Because more than 50% of the controls did not observe the stimulus for 3 and 10 cpd at 0.0085 cd/m^2 and 10 cpd at 0.085 cd/m^2, these data points were omitted. The logCS saturated at different luminances for the different spatial frequencies; the transition luminance was approximately 1, 5, and 60 cd/m^2 for 1, 3, and 10 cpd, respectively. For 1 cpd, the logCS of the controls was lower at 8500 cd/m^2 than at 850 cd/m^2 (paired-samples *t* test; P = 0.003). This is in disagreement with Weber's law. After splitting the healthy subjects in a younger (below median age of 58 years) and older group, the deviation from Webers's law appeared to be present in both subgroups (P < 0.001 and P = 0.02, respectively).

Fig. 2 presents the CS as a function of luminance (Fig. 2A-C) and retinal illuminance (Fig. 2D-F), for the glaucoma patients and age-similar controls. The slopes (95% confidence interval) belonging to the De Vries-Rose law were 0.73 (0.47 to 0.99) and 0.75 (0.51 to 0.99) for 1 cpd, 0.77 (0.51 to 1.03) and 0.87 (0.64 to 1.10) for 3 cpd, and 0.67 (0.40 to 0.95) and 0.55 (0.26 to 0.85) for 10 cpd, for glaucoma patients and controls, respectively (expected slope 0.5; see Section 4).

Obviously, luminance and spatial frequency had an effect on the logCS (both P < 0.001). The effect of glaucoma on logCS depended on luminance (P = 0.003; interaction between glaucoma and luminance in the ANOVA); the overall effect of glaucoma itself did not reach statistical significance (P = 0.14). The effect of glaucoma seemed larger for 3 cpd than for 1 and 10 cpd (Fig. 2), but this difference (interaction between glaucoma and spatial frequency) was not statistically significant (P = 0.27).

4. Discussion

In the central visual field of healthy subjects, Weber's law holds for 3 and 10 cpd, but not for 1 cpd. For 1 cpd, the sensitivity drops under extremely high luminance conditions. The logCS versus log luminance curves did not differ grossly between patients and controls; the difference became larger with decreasing luminance but did not depend clearly on spatial frequency.

The luminance at which the De Vries-Rose transitions into Weber's law (the transition luminance) increased with spatial frequency. Van Nes-Bouman described this relationship and stated that the transition retinal illuminance is directly proportional to spatial frequency squared (Mustonen et al., 1993; Rovamo, Mustonen, & Näsänen, 1994; van Nes, Koenderink, Nas, & Bouman, 1967). We found a transition luminance of 1, 5, and 60 cd/m^2 for 1, 3, and 10 cpd, that is 1, 9, and 100 cpd^2, respectively, which is in good agreement with the above-mentioned relationship. As pointed out by García-Pérez and Peli (1997), the deviation from Weber's law for low spatial frequencies towards higher luminances in healthy subjects is supported by a range of studies. However, these studies addressed a much lower maximum luminance (typically 100 cd/m^2) than we did (10,000 cd/m^2) (Comerford et al., 1987; Daitch & Green, 1969; De Valois et al., 1974; Peli et al., 1996; Rovamo, Mustonen, & Näsänen, 1995; van Meeteren & Vos, 1972). In contrast to these observations, a similar number of studies did not report a lower CS for low spatial frequencies towards 100 cd/m^2, which actually is in agreement with our findings (Coletta & Sharma, 1995; Hess & Howell, 1988; Hess, 1990; Mustonen et al., 1993; Peli, Yang, Goldstein, & Reeves, 1991; Rovamo et al., 1994). Possible explanations for the discrepancy around 100 cd/m^2 could be a difference in stimulus size, a difference in the luminance of the surrounding area, and the small sample size of the majority of the concerning studies (median [IQR] sample size 4 [2 to 5] subjects). Van Nes and Bouman reported no decrease in CS towards higher luminances up to 5900 Td, which is in agreement with our study (Van Nes & Bouman, 1967). Also in agreement with our study is the fact that none of the previous studies reported a deviation from Weber's law for intermediate or high spatial frequencies. This was also reported by Westheimer, who mentioned shortly that he did not see a clear difference between CS measured at 200 and 20,000 Td (actually 5890 Td after recalculation) for intermediate and high spatial frequencies, based on three subjects (Westheimer, 1960). In the De Vries-Rose part of the curve of the controls, the slopes (95% confidence interval) of the logCS as a function of log luminance curves that we measured were 0.74 (0.51–0.96), 0.87 (0.63–1.11), and 0.60 (0.30–0.90) for 1, 3 and 10 cpd, respectively. For 1 and 10 cpd, these slopes are close to the slope of 0.5 from the De Vries-Rose law. The somewhat steeper slope for 3 cpd may reflect lateral inhibition. It has been reported that a slope of 0.5 only holds for small, brief stimuli; for large stimuli of long duration, steeper slopes are found (Barlow, 1972).

Table 2 gives an overview of published literature regarding CS for low (around 1 cpd), intermediate (3–4 cpd), and high (6–30 cpd) spatial

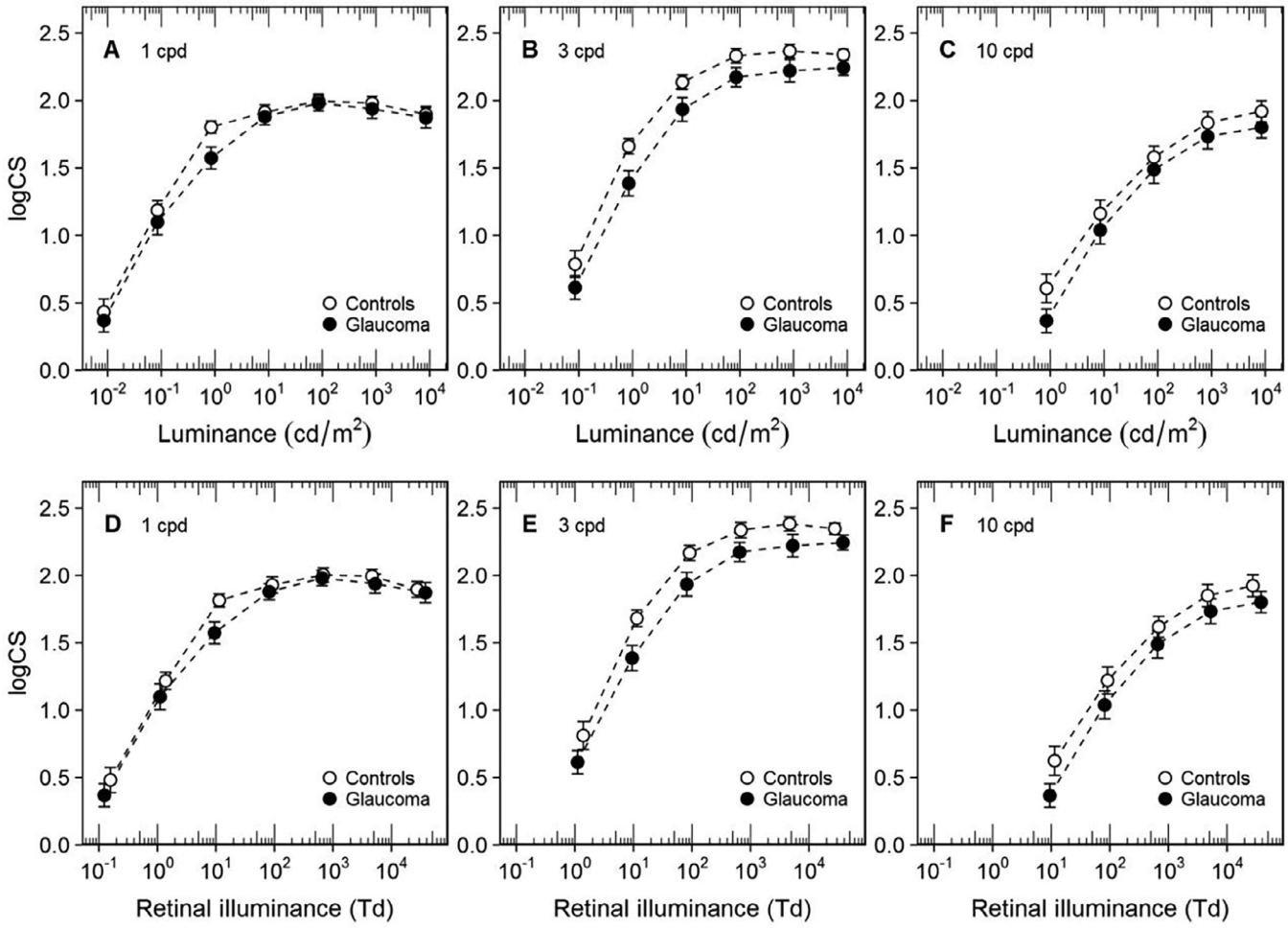

Fig. 2. Spatial contrast sensitivity as a function of luminance (A, B, and C) and retinal illuminance (D, E and F) for glaucoma patients and age-similar controls. Error bars denote ± 1 standard error. The corresponding pupil diameters were 2.5, 3.0, 3.4, 3.9, 4.3, 4.8, and 5.2 mm for the glaucoma patients and 2.1, 2.8, 3.5, 4.2, 4.9, 5.7, and 7.0 mm for the controls.

frequencies in glaucoma patients and controls. Studies were included if they used a sinusoidal stimulus for a series of spatial frequencies. The studies mainly included primary open angle glaucoma patients. Disease severity was omitted because of missing information in almost half of the studies, different assessment techniques, and different definitions. Contrast sensitivity was measured in only one luminance condition, between 15 to 300 cd/m^2. As can be seen in this table, more studies found abnormalities in glaucoma patients at intermediate spatial frequencies than at low spatial frequencies. A typical band-path pattern of the abnormalities (more abnormalities at intermediate frequencies than at low and high frequencies) was not reported in these studies; in our study it seemed to be present (Fig. 2) but was not statistically significant (P = 0.27; see Section 3). Using the same method as we did, Junoy Montolio et al. measured CS for two spatial frequencies at 150 cd/m^2 (Junoy Montolio, Meems, Janssens, Stam, & Jansonius, 2016). They found a decrease in CS in glaucoma patients of 0.2 log unit at 1 cpd (P = 0.008; we found 0.02 log unit), and of 0.3 log units at 4 cpd (P = 0.001; we found 0.2 log unit at 3 cpd). The main difference between the two study populations is the disease stage. The median (IQR) visual field MD was −23.5 (−26.9 to −17.2) dB in Junoy Montolio et al. versus −13.5 (−16.8 to −10.5) dB in our study. This tentatively indicates that involvement of low spatial frequencies is restricted to advanced disease. Interestingly, we found a noteworthy difference of 0.2 log units between glaucoma patients and controls for 1 cpd at 0.85 cd/m^2. There are no studies available to confirm this striking difference at this high-mesopic luminance level (Atchison & Smith, 2002). Only one study measured the spatial CS of glaucoma patients and controls in more than one luminance condition, being 20 cd/m^2 and 0.03 cd/m^2, for one spatial frequency, being 3 cpd (Lahav, Levkovitch-Verbin, Belkin, Glovinsky, & Polat, 2011). Glaucoma patients had a lower CS, at both luminances.

After each change in luminance, we incorporated time to adapt to the new luminance. Hecht et al. reported that, when going from 1000 cd/m^2 to darkness, it takes approximately two minutes to reach a constant threshold for a small central stimulus (Hecht, Haig, & Wald, 1935). Therefore, we assumed that that two minutes of adaptation per log unit decrease in luminance (a much smaller change) should be sufficient to measure adapted cone function. Adaptation to an increase in luminance is much faster, and therefore we chose one minute of adaptation per log unit increase in luminance. The stimulus size (8 by 5 degrees) implies that – at least at 1 cpd – some rod involvement could also be present (3 and 10 cpd are beyond the highest spatial frequency mediated by rods). Rod adaptation, however, takes much longer and for that reason we presumably measured mainly cone function at 1 cpd as well. The relative contribution of rods and cones depends on many factors, and cannot easily be determined in the mesopic range (Stockman & Sharpe, 2006).

We did not dilate the pupil, as we were primarily interested in differences in overall visual function between glaucoma patients and healthy subjects. However, to disentangle the influence of pupil area and luminance, we also presented the graphs as a function of retinal illuminance. We measured the pupil diameter at two luminances in

Table 2
Literature overview regarding contrast sensitivity as a function of spatial frequency in glaucoma.

	Sample size Cases/controls	Mean age (years) Cases/controls	Luminance (cd/m^2)	Setup	Visual Acuity‡ Cases/controls	SF (cpd)	CS Low SF Cases versus controls	CS Intermediate SF Cases versus controls	CS High SF Cases versus controls
Onal 2008	50/20	59/57	85	FACT chart	1.0/1.0	1.5, 3, 6, 12, 18	*Lower*	*Lower*	*Lower*
Ansari 2002	16/16	59/61	120	CRT	≥0.7/M	0.5, 2, 8	*Lower*	M	*Lower*
Horn 1995	59/31	52/47	30	CRT	M/M	0.6, 3, 12	*Lower*	*Lower*	*Lower*
Adams 1987	33/24	65/60	86 (270 lx)	Vistech chart	> 0.5/ > 0.7	1.5, 3, 6, 12, 18	*Lower*	*Lower*	*Lower*
Ross 1984	50/93	70/70	300	Oscilloscope	0.6/0.8	0.4, 1.0, 2.9, 6.7, 12.7, 19.3	*Lower*	*Lower*	*Lower*
Arden 1978	43/50	61/34	130–150	Arden chart	≥0.5/M	0.4, 0.8, 1.6, 3.2, 6.4	*Lower*	*Lower*	*Lower*
Vaegan 1982	43/49	69/63	100	Oscilloscope	0.57/0.75	0.3, 0.5, 1, 2, 4, 8	*Lower*	*Lower*	*Lower*
	24/21	65/61	M	4AFC chart	M/M	0.2, 0.4, 0.9, 1.6, 3.2, 6.4	*Lower*	*Lower*	*Lower*
	24/21	65/61	M	Arden chart	M/M	0.2, 0.4, 0.9, 1.6, 3.2, 6.4	Normal	Normal	*Lower*
Wood 1992	20/20	59/59	290	Oscilloscope	M/M	1, 2, 4, 8, 16	Normal	*Lower*	*Lower*
Sample 1991	31/43	64/60	100–240	Vistech chart	1.0/1.0	1.5, 3, 6, 12, 18	Normal	*Lower*	*Lower*
Korth 1989	32/156	M/M	85	Nicolet CS2000	≥0.3/≥1.0	0.5, 1.0, 3.0, 6.0, 11.4, 22.8	Normal*	Normal*	*Lower**
							Normal†	Normal†	Normal†
Sponsel 1991	31/16	54/53	M	Vistech chart	≥0.5/≥0.5	1.5, 3, 6, 12, 18	Normal	Normal	Normal
Drance 1987	51/28	62/54	M	Nicolet CS2000	M/M	0.5, 1.0, 3.0, 6.0, 11.4, 22.8	Normal	Normal	Normal
Lundh 1985-1	21/11	66/M	120	Oscilloscope	1.0/M	0.5–30	Normal	Normal	Normal
	15/11	68/M	15	Arden chart	0.9/M	0.2, 0.4, 0.8, 1.6, 3.2, 6.4	Normal	Normal	Normal
Lundh 1985-2	14/11	71/M	120	Oscilloscope	1.0/M	0.3, 0.5, 1, 2, 4	Normal	Normal	M
Sokol 1980	20/14	66/66	35	Arden chart	≥0.5/≥0.8	0.4, 0.8, 1.6, 3.2, 6.4	Normal	Normal	Normal

SF = spatial frequency; CS = contrast sensitivity; M = missing.
* Subgroup < 50 years of age;
† Subgroup > 50 years of age;
‡ Mean value or inclusion criteria.

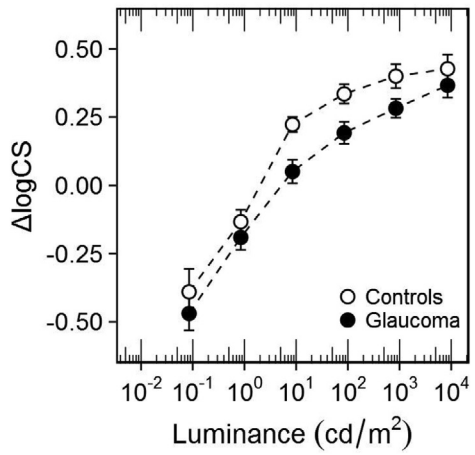

Fig. 3. Difference in logCS between 3 and 1 cpd as a function of luminance, for glaucoma patients and age-similar controls. Error bars denote ± 1 standard error.

order to be able to predict the pupil diameter at other luminances (see Section 2). We did not perform continuous measurements of the pupil diameter during the experiments, because the neutral density filters blocked the infrared radiation of the eye-tracker. As can be seen when comparing the graphs as function of luminance and retinal illuminance, pupil diameter differences had only a minor influence on the shape of the graphs. We adjusted the retinal illuminance for the Stiles-Crawford effect, which limits the effective pupil size for photopic vision (see Section 2). Although this approach has been published already a long time ago (Baron & Enoch, 1982), it is not always used. This is especially important for the interpretation of study results in which a high retinal illuminance was strived for by combining a moderate luminance with a dilated pupil (Mustonen et al., 1993; Rovamo et al., 1994, 1995).

In this study, there was a difference in age distribution between glaucoma patients and controls. We addressed this by using an age-similar subgroup of controls for all analyses where we compared glaucoma with healthy. Therefore, this difference will not have influenced our findings. Strengths of this study are the large luminance range and sample size. Moreover, to the best of our knowledge, this is the first study that measured the CSF in glaucoma patients for a range of luminances. In this study, we covered a range of 6 log units spanning the scotopic to photopic range. The lowest luminance is typically at the lower end of the luminance range that can be found outdoor in the public space after dark (Bierings & Jansonius, 2018); the highest luminance corresponds to the beach at a sunny day at noon and is almost one log unit above the highest luminance condition reported in earlier research, in only one subject (Van Nes & Bouman, 1967).

Our main finding is that the difference in logCS between glaucoma and healthy is rather modest. The difference is more pronounced at lower luminances; the influence of spatial frequency is less clear. At first sight, this suggests a limited impact on glaucoma patients' daily life. As mentioned in the Introduction section, glaucoma patients get symptoms especially under extreme luminance conditions, both low and high, but especially in the dark (Bierings et al., 2018). This agrees with the significant interaction in the ANOVA for glaucoma and luminance ($P = 0.003$), and can also be understood from Fig. 2B. In the De Vries-Rose part of the curve, glaucoma patients need an approximately 0.5 log unit higher luminance than healthy subjects in order to have the same CS, and this increases to 1 log unit around the transition luminance. They never reach the CS of healthy subjects, but they need at least 100 cd/m^2 (corresponding to a well-illuminated office) to have the same CS value as healthy subjects have at 10 cd/m^2 (cosy living room). Abnormalities in contrast adaptation (Dul, Ennis, Radner, Lee, & Zaidi, 2015; Junoy Montolio et al., 2016; McKendrick, Badcock, & Morgan, 2004; Sun, Swanson, Arvidson, & Dul, 2008), a function of the inner retina (Demb, 2008), could also be relevant to patient symptoms.

In a previous study (Bierings et al., 2018), we found larger differences between glaucoma patients and controls for small stimuli (perimetry with Goldmann size III stimulus) than we found in the current study with the 8 by 5 degrees sine-wave patterns. A possible explanation for this difference between the studies is redundancy in the stimulus used in the current study (Howell & Hess, 1978). The redundancy, however, may vary from patient to patient, due to parafoveal defects, which are not uncommon in patients with an apparently intact central visual field according to their visual acuity and standard automated perimetry test results (Asaoka, 2014; De Moraes et al., 2017; Grillo et al., 2016; Hood et al., 2011; Park et al., 2013; Schiefer et al., 2010; Traynis et al., 2014). With spatial integration over 5 to 10 cycles (Howell & Hess, 1978), small parafoveal defects might compromise CS assessed with 3 cpd gratings more than CS assessed with 1 or 10 cpd gratings.

As mentioned in the Introduction section, a healthy visual system performs spatial low-pass filtering at low luminances and spatial band-pass filtering at high luminances (van Hateren, 1992). This can be seen in Fig. 1. At approximately 2 cd/m^2, the CS at 3 cpd surpasses the CS at 1 cpd, indicating the transition to band-pass filtering. In the study of van Nes and Bouman, the transition happened between 0.9 and 9 Td at a pupil diameter of 2 mm (that is, between 0.3 and 3 cd/m^2), which is in agreement with our results. The question is if and how this transition happens in glaucoma. Fig. 3 shows the difference in logCS between 3 and 1 cpd as a function of luminance, for glaucoma patients and age-similar controls. As can be seen in this figure, logCS 3 versus 1 cpd follows the same pattern in glaucoma patients and controls, but the transition occurs at an approximately 0.5 log unit higher luminance and there is a vertical gap of approximately 0.1 log unit between both groups, roughly independent of the luminance. This is in agreement with Junoy Montolio et al., who found a (nonsignificant) difference of 0.079 log unit between glaucoma patient and healthy controls at 150 cd/m^2 (Junoy Montolio et al., 2016). Band-pass filtering plays a role in detection of edges (Jansonius & Kooijman, 1997; King-Smith & Kulikowski, 1975). Edges (or contours) are, unlike sine-wave patterns, very common features of natural images. For that reason, differences in the transition from low-pass to band-pass filtering may have a relevant impact.

In conclusion, we described visual function in healthy subjects and glaucoma patients over a wide range of luminances. Differences between glaucoma and healthy were relatively modest for the spatially redundant, static stimulus as used in the current study, with some increase in difference towards the lower luminances. As mentioned in Section 1, glaucoma patients do complain regarding their visual performance under low, high, or changing luminance conditions, with the low luminance condition as the most cumbersome one (Bierings et al., 2018). Complaints under the low luminance condition could be explained by the fact that visual performance drops down in everyone when going from twilight to starlight; glaucoma patients will cross a certain minimum CS needed for reasonable vision earlier than healthy subjects. Complaints under the high luminance condition cannot be explained from our results directly, as the difference between glaucoma and controls was at least as large at intermediate luminances, for which glaucoma presents itself as asymptomatic. The influence of changing luminance conditions was not addressed in the current study – we aimed to reach a steady state by employing adaptation time between the measurements. Hence, future research could focus on the dynamic properties of light and dark adaptation in glaucoma.

Conflict of interest

None.

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