INSIGHT IN TO LIGHT

The influence of luminance on visual functioning in glaucoma

Ronald A.J.M. Bierings

University of Groningen

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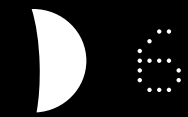

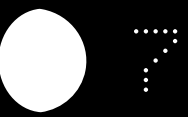

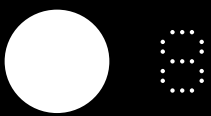

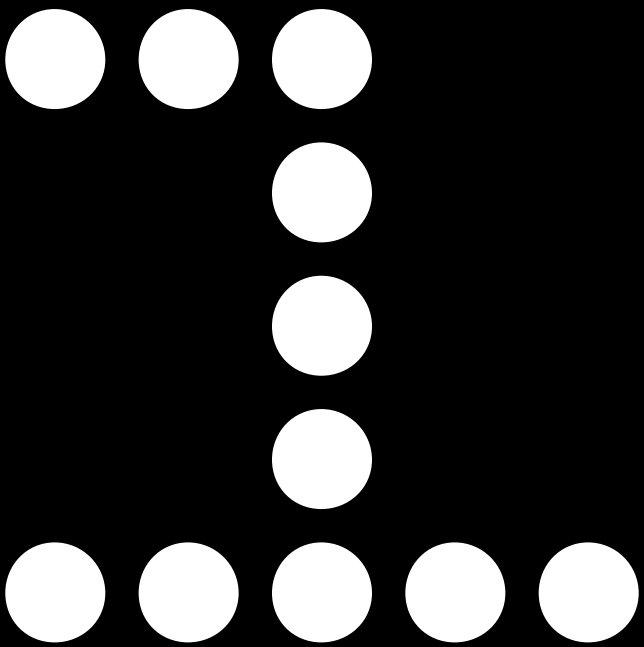

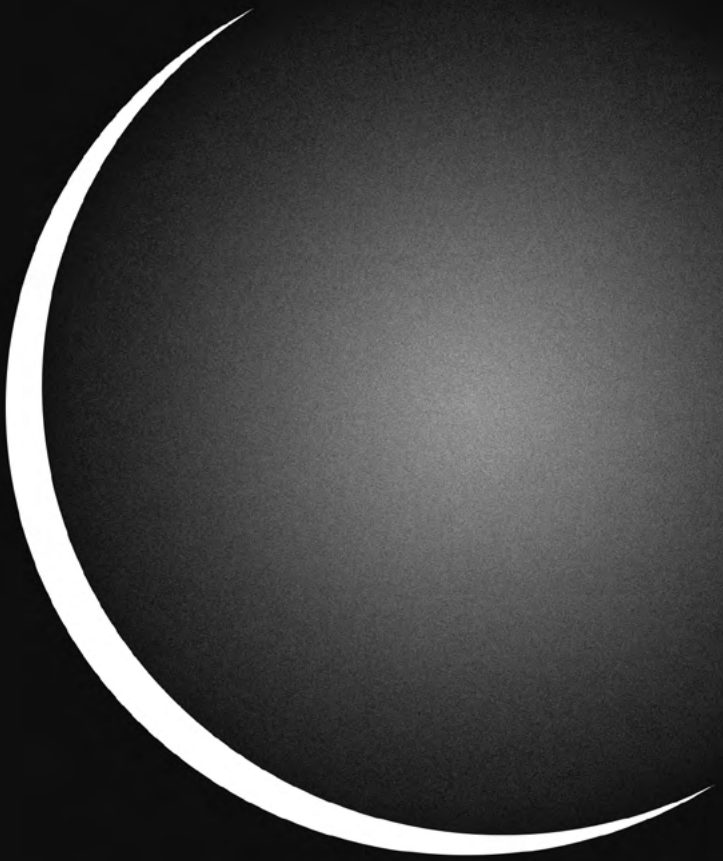

GENERAL INTRODUCTION

For a human being, vision is presumably the most important of the physical senses to perform daily activities. Loss of vision limits participation in society and decreases quality of life.[1–3] Eye diseases like glaucoma are more common in the elderly; a population that will almost double the upcoming decades.[4] Therefore, investing in the study of eye diseases and the interaction of ophthalmic patients with their environment is essential.

This general introduction will provide you with the background information to appreciate how the two main themes of this thesis - glaucoma and light - come together in the main objective of this thesis. First, **glaucoma** as an eye disease will be introduced. Second, some day-to-day examples will provide context for the **physical quantities of light** used in the experiments. Third, the physiology of **light and dark adaptation** gives some basic insight on how the visual sensitivity remains optimal under different light conditions. Fourth, **contrast sensitivity** as a measure to quantify visual sensitivity will be discussed. Finally, the available knowledge on the visual function of **glaucoma patients under extreme luminances** will serve as a prelude to the **aims and outline of this thesis**.

GLAUCOMA

Vision starts with light that passes through the cornea, the pupil, the lens, the vitreous body, and eventually reaches the retina. Photoreceptors in the retina convert light into an electric signal that is transferred through the optic nerve to the brain. After the signal is processed and interpreted, our brain forms the image we see of the outside world. Glaucoma is a chronic and progressive eye disease in which the optic nerve is damaged. This is characterized by the loss of retinal ganglion cells (RGCs) and thinning of the retinal nerve fiber layer (RNFL). Consequently, the visual field is damaged, typically starting in the periphery.[5] There are different forms of glaucoma, of which the most common form in Caucasians is Primary Open Angle Glaucoma (POAG).[6] As the research performed in this thesis primarily concerns patients with POAG, POAG from this point on will be referred to as 'glaucoma'. Glaucoma has a prevalence of 2% and is the leading cause of irreversible blindness in the world.[7] The most important risk factor for glaucoma is an increased intraocular pressure; the combination with a suspicious-appearing optic nerve and an abnormal visual field establishes the diagnosis.[8] Other risk factors include older age, myopia, and a positive family history for glaucoma.[9,10] Decreasing the intraocular pressure is the only effective treatment currently available.[11,12] Glaucoma follow-up consists of the measurement of the intraocular pressure, and the assessment of the optical nerve head, the visual field (perimetry), and the RNFL.[8]

The early detection of glaucoma is crucial, as damage to the optic nerve and the subsequent visual field cannot be undone. However, the disease course is insidious, leading to a delay between the onset and the diagnosis of glaucoma. This is a consequence of the inability of patients to physically perceive high intraocular pressure, which would have urged them to go to an ophthalmologist. In addition, visual field loss in one eye can be compensated for by information from the other eye, and masked by the brain's ability to 'fill in' the damaged parts of the visual field.[13] Therefore, glaucoma

patients are considered to be asymptomatic, and often unaware of their disease until at a late stage.[5] However, patients may have been experiencing visual symptoms at an early stage that we did not yet recognize as related to glaucoma. *In the ophthalmology outpatient clinic, glaucoma patients themselves spontaneously reported poor vision under low, high, and changing light conditions as symptom. Therefore, the study to the influence of light conditions on visual functioning in glaucoma, which will be described in this thesis, was a logical step.*

PHYSICAL QUANTITIES OF LIGHT

To appreciate what low and high light conditions are, some knowledge regarding the physical quantities used to describe the amount of light is necessary. The visible part of the electromagnetic spectrum is called light. On the box of a light bulb, the amount of light reported is in lumens. Especially with the traditional incandescent bulb, a significant amount of power consumed (i.e., energy per time expressed in Watts, or Joules per second) is converted into heat. The amount of power that is converted into light is expressed in lumens (lm), which is the unit of luminous flux. The luminous flux that is incident on a surface of one square meter is called illuminance, which is expressed in lux (lm/m^2). Although these physical quantities are indicative for the amount of light, the luminous flux and illuminance are not what we perceive. What we perceive is the amount of illuminance that is reflected by a surface: the luminance in candela per square meter (cd/m^2). In the case of a perfectly diffusely reflecting surface (Lambertian reflectance), the luminance can be calculated by dividing the illuminance by π (Lambert's cosine law). Because light is also partially absorbed by a surface, the resulting value is multiplied by a reflection factor (reflectance). The advantage of using luminance as the physical quantity of light, is that it is independent of the distance. Finally, the actual amount of light on our retina is influenced by pupil size. Therefore, the luminance is multiplied by the pupil area in square millimeter to obtain the retinal illuminance in Troland (Td).

In the experiments of this thesis, we mainly focus on the luminance as the physical quantity of light. To give an idea of luminances in daily life: a white paper under starlight has a luminance of $\sim$0.001 cd/m^2, under moonlight $\sim$0.01 cd/m^2, under indoor lighting $\sim$100 cd/m^2, and under sunlight $\sim$10,000 cd/m^2. Some possibly more applicable examples from 21st century daily life: the luminance of a white text document on a computer screen is usually $\sim$150 cd/m^2, and the luminance of a white screen of a 2.5 year old iPhone 5s can be adjusted from $\sim$3 to $\sim$350 cd/m^2.

LIGHT AND DARK ADAPTATION

Light and dark adaptation allows the visual sensitivity to remain optimal over a wide range of luminances.[14] Since the luminance under starlight is about 10^7 times lower than the luminance under sunlight, adaptation is a crucial prerequisite for vision in daily life.[15–17] While pupil size and neural adaptation have a modest role, the most important factor in adaptation is based on photochemistry in photoreceptors (cones and rods). Photoreceptors contain light-sensitive and light-insensitive photopigment.

When adapted to high luminances, a large amount of the photopigment is reduced to the light-insensitive form ('bleaching'). The reduced concentration of light-sensitive photopigment in the cones and rods leads to a reduced sensitivity of the eye to light. When adapted to low luminances, the light-sensitive photopigment is regenerated which – consequently – increases the sensitivity of the eye to light.[18] Rods are more sensitive to light than cones; unlike cones, rods will be completely completely depleted of light-sensitive photopigment ('bleached') at high luminances. Therefore, only cones are responsible for photopic vision (>3 cd/m^2), both cones and rods for mesopic vision (0.03-3 cd/m^2), and only rods for scotopic vision (<0.03 cd/m^2).[19] Although rods are more sensitive to light, the chemical regeneration of photopigment occurs four times as slow compared to the pigment in cones. The implication of the sensitivity and recovery speed of cones and rods come together in the dark adaptation curve (Fig. 1), which shows the sensitivity of the eye as a function of time after exposure to an extremely high luminance. The initial, rapid increase in sensitivity is caused by dark adaptation of the cones. After this cone adaptation, rods catch up and achieve a much higher sensitivity. The solid line represents the resulting retinal sensitivity of both cones and rods. The dark adaptation curve explains why we almost immediately see something when going into the dark, but need more time to fully employ our visual sensitivity.

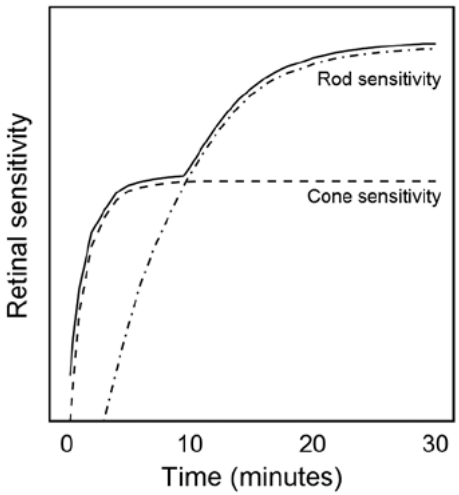

Figure 1. *Retinal sensitivity as a function of time after exposure to an extremely high luminance (i.e., the dark adaptation curve). The initial, rapid increase in sensitivity is caused by dark adaptation of the cones. After this cone adaptation, the rods catch up and achieve a much higher sensitivity. The solid line represents the resulting retinal sensitivity of both cones and rods.*

CONTRAST SENSITIVITY

A common method to quantify visual sensitivity is by means of the contrast sensitivity. Contrast sensitivity (CS) is defined as the smallest luminance difference that a visual system is able to detect. Luminance differences are described by means of contrast. Contrast can be calculated in two ways: (1) contrast for small stimuli on large uniform

backgrounds (Weber contrast; see the front cover of this thesis), and (2) contrast for gratings (Michelson contrast; Fig. 2). In the experiments of this thesis, both Weber and Michelson contrast will be used. The CS is the reciprocal of the smallest detectable contrast (the threshold contrast). In formula:

(1) Weber contrast: $\frac{L_s - L_b}{L_b}$

(2) Michelson contrast: $\frac{L_{max} - L_{min}}{L_{max} + L_{min}}$

Contrast sensitivity: $\frac{1}{|\ treshold\ contrast\ |}$

where L_s is the luminance of the stimulus, L_b the luminance of the background, L_{max} and L_{min} the maximum and minimum luminance within the grating. The CS is commonly reported as the logarithm to base 10 of the CS: the logCS.

CONTRAST SENSITIVITY & SPATIAL FREQUENCY

The CS is dependent on the spatial characteristics of stimuli, which can be assessed by using gratings of different widths. The width of a grating can be described by the spatial frequency: the number of cycles (black and white bars) per degree of visual angle (cpd). To illustrate, one degree of visual angle subtends approximately the width of the index fingernail at arm's length. A low spatial frequency (e.g., 1 cpd) means broad bars, whereas a high spatial frequency (e.g., 10 cpd) means thin bars (Fig. 2).

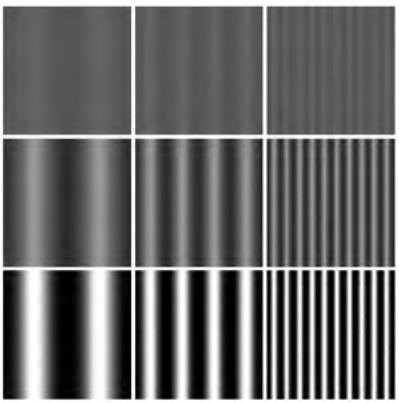

Figure 2. *Vertically oriented sine-wave gratings. Spatial frequency increases from left to right. Contrast increases from top to bottom.*

The logCS as a function of spatial frequency is called the contrast sensitivity function (CSF; Fig. 3). The maximum of the CSF is caused by processing of visual information by the RGCs, called lateral inhibition. Lateral inhibition starts with the area on the retina over which the firing rate of an RGC is influenced: the receptive field. Light that falls only on the center of the receptive field increases the firing rate; light that falls only

on the surround decreases it. When light falls on both the center and the surround, the excitation from the center is inhibited by the surround, and the firing rate remains unchanged.[15] Because of lateral inhibition, the human retina is the most sensitive to gratings that excite only the center of the receptive field. At high luminances, this occurs around a spatial frequency of 3-4 cpd.[20] Towards lower and higher spatial frequencies, the CS decreases because light falls on both the excitatory center and inhibitory surround of the receptive field. At higher spatial frequencies, the logCS decreases even further because of the acuity limits of the visual system.[15]

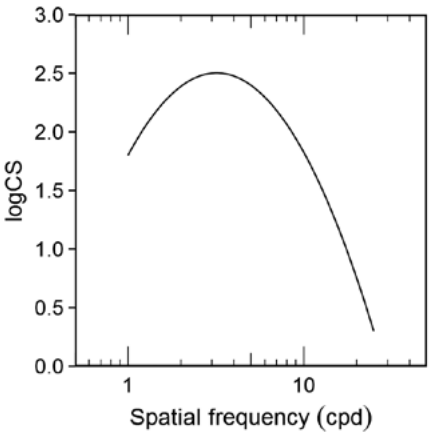

Figure 3. *The logCS as a function of spatial frequency (i.e., the contrast sensitivity function). The maximum of the CSF at 3-4 cpd is caused by lateral inhibition (see text). Towards lower and higher spatial frequencies, the CS decreases because of reduced lateral inhibition. At higher spatial frequencies, the logCS decreases even further because of the acuity limits of the visual system.*

CONTRAST SENSITIVITY & LUMINANCE

In addition to its dependence on the spatial frequency, the CS is also influenced by the luminance condition under which it is measured. The CS as a function of spatial frequency and luminance in healthy subjects is established by the research field that studies the relation between stimulus and perception, so called psychophysics. When measuring the CS at different luminances, two major psychophysical laws are applicable (Fig. 4):

(1) the De Vries-Rose law: the CS is proportional to the square root of the luminance at low luminances.[21,22]

(2) Weber's law: the CS is constant at high luminances.[23]

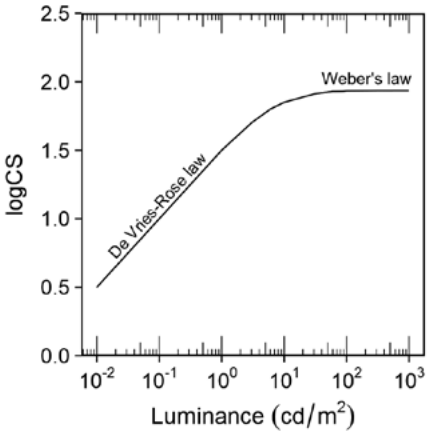

Figure 4. *The logCS as a function of luminance. At low luminances, the CS is proportional to the square root of the luminance (the De Vries-Rose law). At high luminances, the CS is constant (Weber's law).*

GLAUCOMA PATIENTS UNDER EXTREME LUMINANCES

To summarize, glaucoma is characterized by the loss of RGCs and visual field defects, the wide range of luminances in daily life are processed by adaptation, and the CS can be used to quantify visual sensitivity. What is there still to unravel?

1. Subjective visual function
Although glaucoma patients are considered to be asymptomatic, fragmentary findings revealed that they seem to experience visual difficulties under extreme (low, high, or rapidly changing) luminance conditions.[24–29] This might suggest an impaired light and dark adaptation, which would be an intriguing finding, because the cones and rods – rather than the RGCs – are thought to be the primary site of adaptation.

2. Objective visual function
It is generally accepted that glaucoma patients have a lower CS compared to healthy subjects.[30–39] However, previous studies that included glaucoma patients measured the visual function only at one comfortable luminance condition, and not towards the extremes. If the difference between glaucoma patients and healthy subjects in extreme luminances is indeed more pronounced, this may be helpful for improving diagnostic tests and commencing treatment earlier.

AIMS AND OUTLINE OF THIS THESIS

The main objective of this thesis is to unravel the effect of luminance on visual functioning in glaucoma patients. We specified our objective into two primary aims:

(1) To determine the effect of luminance on **subjective** visual functioning in glaucoma.
(2) To determine the effect of luminance on **objective** visual functioning in glaucoma.

Apart from influencing visual responses to light, glaucoma might also influence nonvisual responses to light, such as the sleep-wake cycle. In healthy subjects, the circadian clock is entrained to light by the input of a special type of RGCs: the intrinsically photosensitive RGCs (ipRGCs). Loss of ipRGCs in glaucoma patients might result in a lower susceptibility of the circadian clock to light and a change in the sleep-wake cycle. Therefore, we explore the influence of glaucoma on the chronotype (the midpoint between sleep onset and wake-up time on days off), which is a marker for the circadian phase.

This thesis focuses primarily on the difference in visual functioning between glaucoma patients and healthy subjects. Therefore, all projects – except for the citizen science project in Chapter 6 – included a group of glaucoma patients and controls. In **Chapter 2**, a newly developed questionnaire is used to determine the effect of luminance on subjective visual functioning. **Chapter 3** describes the applicability of the above mentioned psychophysical laws. In **Chapter 4**, the visual function from star- to sunlight is objectified by means of the contrast sensitivity at different spatial frequencies. **Chapter 5** describes the results of the traditional light and dark adaptation experiment. In **Chapter 6**, a citizen science network of smartphone users provides information about the relation between visual complaints and luminances from real-life environments after dark. **Chapter 7** focuses on the chronotype. Finally, the summary and general discussion in **Chapter 8** summarizes the most important findings, connects subjective to objective visual functioning of glaucoma patients at different luminances, discusses the clinical implications of our findings, and provides recommendations for future research.

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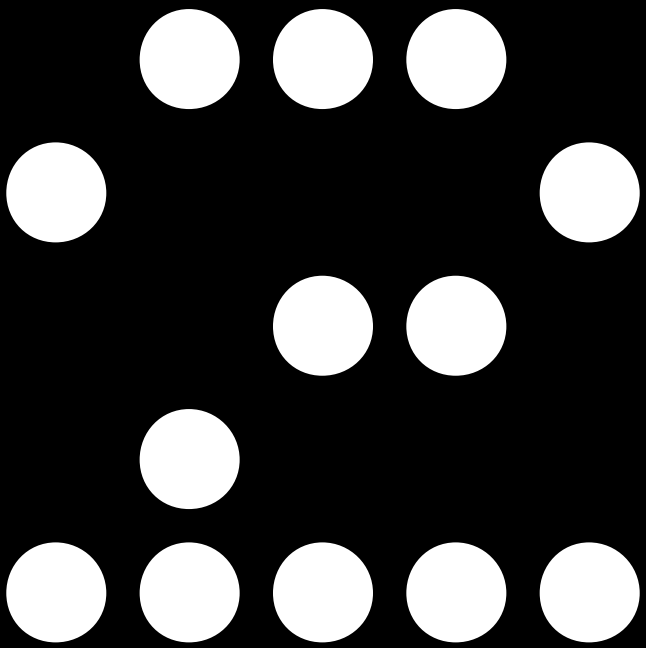

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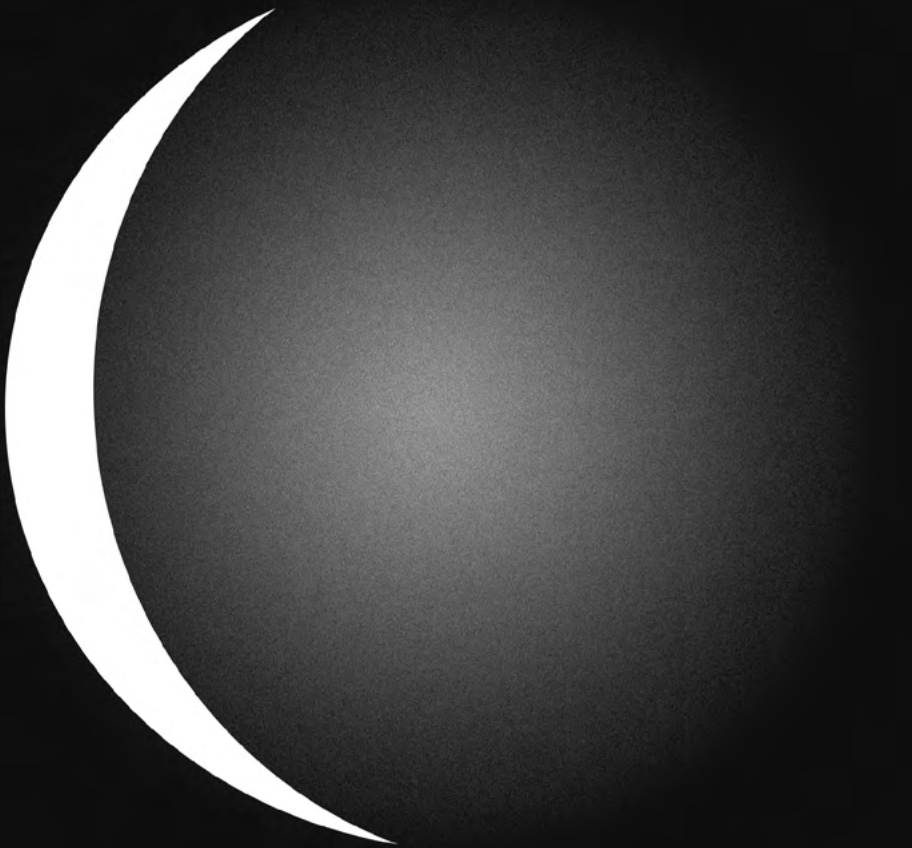

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VISUAL COMPLAINTS OF PATIENTS WITH GLAUCOMA AND CONTROLS UNDER OPTIMAL AND EXTREME LUMINANCE CONDITIONS

ABSTRACT

Purpose: To determine (1) whether, compared to controls, visual complaints of glaucoma patients are more pronounced under extreme luminance conditions than in the optimal luminance condition and (2) whether complaints belonging to different extreme luminance conditions are associated.

Methods: We developed a luminance-specific questionnaire and sent it to 221 glaucoma patients (response rate 81%); controls (182) were primarily their spouses. Median (interquartile range) mean deviation of the visual field of the patients' better eye was -4.5 (-10.7 to -1.9) dB. Questions were addressing visual performance under five luminance conditions: presumed optimal (outdoor on a cloudy day), low, high, sudden decrease, and sudden increase. We compared percentages of patients and controls who reported visual complaints while performing activities under different luminance conditions.

Results: Percentages of patients and controls with visual complaints were 4 versus 0% (P=0.02) for optimal luminance and 48 versus 6% (P<0.001), 22 versus 1% (P<0.001), 32 versus 1% (P<0.001), and 25 versus 3% (P<0.001) for low, high, sudden decrease, and sudden increase in luminance. Within the group of glaucoma patients, the frequency of complaints increased significantly with increasing disease severity at a Bonferroni-corrected P value of 0.003 for all but one (P=0.005) luminance-specific questions that addressed extreme luminance conditions.

Conclusions: The concept of (early-stage) glaucoma as an asymptomatic disease is only valid with optimal luminance. Differences in visual complaints between glaucoma patients and controls are greater under extreme luminance conditions, especially in the dark. The fact that the cases were aware of their diagnosis could have induced bias.

INTRODUCTION

Glaucoma is a chronic and progressive eye disease characterized by loss of retinal ganglion cells (RGCs) and subsequent visual field loss. Visual field loss in glaucoma has traditionally been described as asymptomatic, peripheral visual field loss.[1] Although glaucoma indeed seems to be an asymptomatic disease in an early stage, glaucoma patients do report complaints; not related to peripheral visual field loss but to visual performance under extreme (low, high, or changing) luminance conditions.[2–7] Complaints under extreme luminance conditions suggest impaired dark and light adaptation in glaucoma, which is an intriguing finding, because the rods and cones rather than the RGCs are the primary site of adaptation. A thorough understanding of the complaints could thus be important for a better understanding of the patient, the physiology of the retina, the pathophysiology of glaucoma, and for improving diagnostic tests.

An increase in complaints under extreme luminance conditions is, in itself, not a surprise – this may also occur in healthy subjects; the question is whether the difference in visual complaints between glaucoma patients and healthy subjects is more pronounced under extreme luminance conditions compared to the optimal luminance condition. To address this question, it is necessary to have both an appropriate control group and a questionnaire with an extensive set of luminance-specific questions. None but two[5,7] of the earlier studies did include a control group; without exception, earlier studies only included a subset of luminance conditions, and questions regarding the optimal luminance condition were always omitted. Another important question is whether complaints under low, high, and changing luminance conditions go together (and may be thus related to a single underlying defect) or may appear in different proportions in different patients. Finally, if indeed the difference in visual performance between glaucoma patients and controls is more pronounced under extreme luminance conditions than under the optimal luminance condition, it might be better to perform diagnostic tests under extreme luminance conditions.

The aim of this study was to determine (1) whether, compared to controls, visual complaints of glaucoma patients are more pronounced under extreme luminance conditions than in the optimal luminance condition and (2) whether complaints belonging to different extreme luminance conditions are associated. For this purpose, we performed a questionnaire study with an extensive set of luminance-specific questions amongst a large group of glaucoma patients and controls.

METHODS

Study population and data acquisition

We sent a questionnaire by mail to 221 glaucoma patients with primary open-angle glaucoma, pseudoexfoliation glaucoma, or pigment dispersion glaucoma. Patients were selected from the database of the Groningen Longitudinal Glaucoma Study, an observational cohort study conducted in our department.[8] We approached those participants who still were regular visitors of the outpatient clinic, were followed with standard automated perimetry (SAP; Humphrey field analyzer [HFA] 30-2 SITA; Carl Zeiss Meditec AG, Jena, Germany), and had a reproducible visual field defect on SAP in at least one eye, defined as a scotoma according to the LTG-P criterion[9] or a glaucoma hemifield test 'outside normal limits'. For descriptive statistics, the patients were stratified into early, moderate, or severe glaucoma, using the mean deviation (MD) value of the better eye (eye with the higher MD value).[10–15] As cut-off points between the strata we employed -6 and -12 dB. For the classification, we used the most recent visual field test result. The median (interquartile range [IQR]) time window between this visual field and the questionnaire completion was 6 (2 to 14) months. We did not exclude visual fields based on reliability (in order to keep the time window as short as possible). The percentage of false positive responses, the only reliability index that is significantly associated with the MD,[16,17] was ≤10% in 165 of 178 glaucoma patients who returned the questionnaire. The median (IQR) percentage of false positive responses was 13 (12-17) % in the remaining 13 patients. Patients were not selected with regard to their glaucoma stage.

Two questionnaires were sent to each patient; they were asked to complete one questionnaire and to give the other to their spouse, neighbor, friend, etc. (no consanguinity), who served as control. Patients and controls were explicitly asked to fill in the questionnaire independently. As the number of returned patient questionnaires exceeded the number of control questionnaires, additional controls were recruited from a recent case-control studies conducted in our department.[18] Controls were asked to confirm that they (1) did not have relatives with high eye pressure or glaucoma and (2) did not receive regular checkups by an ophthalmologist for high eye pressure or glaucoma. In this way we assured a glaucoma prevalence of <1% amongst the controls.[19]

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.

Questionnaire

The questionnaire was developed to explore visual complaints during activities of various difficulty, under optimal and extreme luminance conditions. We did not develop a questionnaire from scratch but used questions from existing glaucoma-related questionnaires (GQL[6] and GSS[5]) and the NEI-VFQ25,[20,21] and extended them to the different luminance conditions. The development followed the six constructive guidelines of de Vet et al., including a pretest in 13 healthy subjects and 2 glaucoma

patients using the Three-Step Test-Interview.[22,23] In short, this method implies that (Step 1) respondents were asked to think aloud, and their behavior was observed while filling in the questionnaire (hesitation, skipping questions, corrections of the chosen response category, etc.). After that (Step 2), we interviewed the respondents to clarify the observations (e.g., 'You stopped for a while, why?'). Finally (Step 3), we asked for experiences and opinions. Here, we also explicitly asked to describe the situations they imagined while filling in the specific questions.

The questionnaire included 15 luminance-specific questions addressing visual performance under five different conditions: (1) presumed optimal luminance (outdoor on a cloudy day, four questions), (2) low luminance (outdoor at night, three questions), (3) high luminance (outdoor on a sunny day, four questions), (4) sudden decrease in luminance (two questions), and (5) sudden increase (two questions). Within the questionnaire, the questions were ordered by activity (e.g. seeing, walking/cycling, driving), starting with the question regarding the high luminance condition, then optimal, low, and ending with questions regarding the changing luminance conditions. The questionnaire was developed in Dutch.

Data analysis

Glaucoma patients and controls had a different age distribution. To enable a fair comparison between the groups, we equalized the number of patients and controls per age bin of ten years, by applying a weight factor. For example, if in a certain age bin there were twice as many controls as cases, the controls were entered in the analysis with a weight factor of 0.5. Similarly, if there were more patients than controls in a certain age bin, the patients were entered with a weight factor <1. In this way, the effective number of subjects decreased slightly, but the weighted subjects formed age-matched groups.

Questions regarding visual complaints contained five response options. For the initial descriptive analysis, we dichotomized these response options into 'No complaints' and 'Complaints'. The answer options 'No difficulty at all' and 'A little difficulty' became 'No complaints'; 'A lot of difficulty', 'Extreme difficulty', and 'Stopped doing this because of my eyesight' became 'Complaints'. Every question also had an answer option 'Not applicable', which we considered as missing during analysis. We calculated, per question, the percentage of complaints within the group of glaucoma patients and controls, and the corresponding difference with 95% confidence interval (CI). We compared the percentage of complaints between the groups with chi-squared tests with Bonferroni correction. We considered the difference between the groups as clinically relevant if the difference was both statistically significant and at least 10%. Similarly, if this difference was at least 10% larger under extreme luminance conditions compared to the difference with optimal luminance, we considered the complaints of glaucoma patients as disproportionately more pronounced under extreme luminance conditions. The value of 10% is to a certain extent arbitrary, but prevents emphasis on small differences that may be statistically significant, but not clinically relevant. We used a chi-squared test for trend with Bonferroni correction to determine whether complaints were more frequent with increasing disease severity within the group of glaucoma patients.

Not all tasks (e.g., reading) can be done under all luminance conditions. To enable a fair comparison between all luminance conditions, we selected, for each luminance condition, one question that did not refer to a specific task, i.e. seeing or adapting. For those luminance conditions with more than one 'task-independent' question available, we chose the question that differentiated best between glaucoma patients and controls.

To determine whether complaints from the four extreme luminance conditions (low, high, sudden decrease, sudden increase) were associated, we used the selected task-independent questions (see above), made 2x2 tables, and calculated Phi coefficients for each combination of conditions, for the glaucoma patients. Differences between the conditions were evaluated with McNemar's test with continuity correction.

We considered a P value of 0.05 or less statistically significant. Bonferroni correction was applied if applicable.

RESULTS

We retrieved 178 questionnaires from 221 glaucoma patients (response rate 81%) and 182 questionnaires from controls. The mean (standard deviation [SD]) age of the glaucoma patients was 72.2 (10.0) years and of the controls 65.7 (10.8) years. After weighting, both groups had a size of 135 subjects, with a mean (SD) age of 69.6 (9.3) years for the glaucoma patients and 69.0 (9.3) years for the controls (P=0.63). The glaucoma patients consisted of fewer females compared to the controls (47% versus 64%; P=0.01). Most of the patients had early glaucoma (62%); about one-third had either moderate (16%) or severe (22%) glaucoma in the better eye. The median (IQR) HFA MD of the better eye was -4.5 (-10.7 to -1.9) dB. Most of the glaucoma patients (80%) had a pretreatment intraocular pressure of 21 mmHg or more.

Figure 1 shows two examples of responses to the questions 'Seeing outside on a cloudy day' (left panel) and 'Seeing outside at night when there is no moonlight' (right panel). The upper row presents all response options for controls and patients; the lower row presents the dichotomized responses for controls and patients with increasing disease severity.

Table 1 presents the dichotomized results for the 15 included questions, categorized in five luminance conditions. The table shows the percentages of patients with glaucoma and controls who reported complaints, and the corresponding differences. Within each luminance condition, the questions were ranked according to these differences. All questions resulted in a significant difference between glaucoma patients and controls at a Bonferroni-corrected P value of 0.003 (0.05/15), except for 'Walking or cycling on a cloudy day' (P=0.01) and 'Seeing outside on a cloudy day' (P=0.02). Two of four questions regarding the optimal luminance condition resulted in a clinically relevant difference (for definition, see Methods section) between glaucoma patients and controls; all questions regarding the extreme luminance conditions resulted in a clinically relevant difference between glaucoma patients and controls.

Within the group of glaucoma patients, the frequency of complaints increased significantly with increasing disease severity at a Bonferroni-corrected P value of 0.003 (0.05/15) for all luminance-specific questions, except for 'Seeing outside on a cloudy day' (P=0.28) and 'Seeing outside on a sunny day' (P=0.005).

The five task-independent questions were marked in Table 1 with a *. The difference between the groups for these questions under extreme luminance conditions, compared to the optimal luminance condition, was more than 10%. That is, visual complaints of glaucoma patients were, compared to controls, disproportionately more pronounced under extreme luminance conditions.

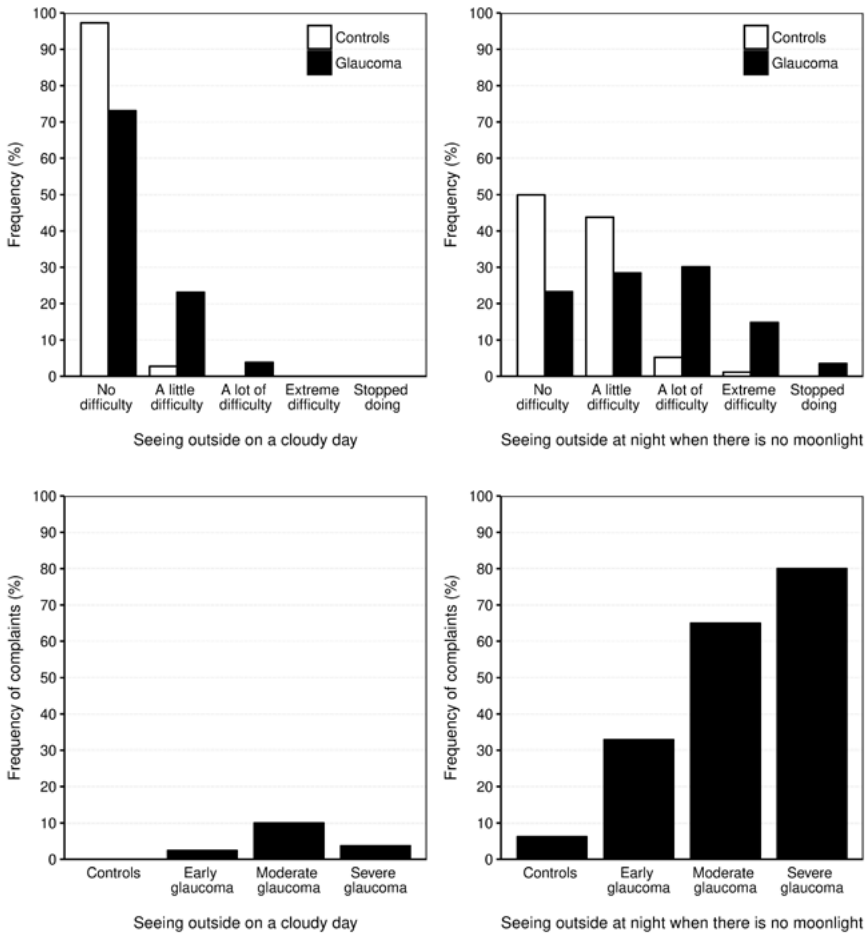

Figure 1. Examples of responses to the questions. Left panel: 'Seeing outside on a cloudy day'; right panel: 'Seeing outside at night when there is no moonlight'. Upper row: all response options for controls and glaucoma patients; lower row: dichotomized responses for controls and glaucoma patients with increasing disease severity.

Table 1. Percentages of glaucoma patients and controls who reported complaints, per question; questions were ranked, per category, according to the differences between glaucoma patients and controls.

Questions ordered by luminance condition. All questions were preceded by 'Because of your eyesight, how much difficulty do you have with...'. If applicable, subjects were asked to answer the questions as if they were wearing their glasses or contact lenses.	Complaints (%)			Missing (%)
	Glaucoma	**Controls**	**Difference** (95% CI)	**Glaucoma versus controls**
Presumed optimal luminance				
Driving on a cloudy day	14.4	0	14.4 (7.6-21.3)	23.0/14.8
Reading outside on a cloudy day	11.4	0	11.4 (5.8-17.0)	5.9/3.0
Walking or cycling on a cloudy day	4.3	0	4.3 (0.8-7.9)	5.9/2.2
Seeing outside on a cloudy day *	3.8	0	3.8 (0.5-7.1)	3.7/1.5
Low luminance				
Seeing outside at night when there is no moonlight *	48.4	6.3	42.1 (32.1-51.9)	9.6/3.7
Walking or cycling at night on an unlit country road	53.6	13.7	39.9 (28.7-51.2)	16.3/14.1
Driving at night on an unlit country road	49.7	12.7	37.0 (25.2-48.9)	26.7/20.7
High luminance				
Reading outside in the sun	34.3	3.9	30.4 (21.5-39.4)	5.2/2.2
Seeing outside on a sunny day *	22.2	1.3	20.9 (13.5-28.3)	2.2/1.4
Walking or cycling on a sunny day	18.7	0.6	18.1 (11.2-25.1)	5.2/2.2
Driving on a sunny day	20.2	1.7	18.5 (10.2-26.8)	25.9/17.0
Sudden decrease in luminance				
Adapting to dim lights, when coming from a well-lit environment *	32.4	0.8	31.6 (23.3-39.9)	3.7/3.0
Adapting to less light, when coming from the bright sunlight	24.9	1.3	23.6 (15.8-31.4)	4.4/3.0
Sudden increase in luminance				
Adapting to bright sunlight, when coming from less light *	25.0	2.7	22.3 (14.3-30.3)	3.7/3.7
Adapting to a well-lit environment, when coming from dim lights	13.0	0.8	12.2 (6.2-18.3)	3.7/3.0

* = selected task-independent question (see Methods section).

Figure 2 shows the difference in complaints between glaucoma patients and controls for the five task-independent questions, stratified by gender. The most obvious difference in the difference between glaucoma patients and controls was found between the optimal luminance condition and the low luminance condition, for both genders. Generally, the differences were more pronounced in women than in men. Male and female glaucoma patients had similar MD values of the better eye (P=0.26, Mann-Whitney U).

Table 2 presents the 2x2 tables and corresponding Phi coefficients describing the association between the selected task-independent questions belonging to the four extreme luminance conditions, for the glaucoma patients. All Phi coefficients were significant at a Bonferroni-corrected P value of 0.008 (0.05/6); they varied between 0.40 and 0.62. McNemar's test showed a significant difference at a Bonferroni-corrected P value of 0.008 (0.05/6) for low versus high, low versus sudden decrease, and low versus sudden increase (all P<0.001), uncovering the low luminance condition as the most difficult condition for glaucoma patients.

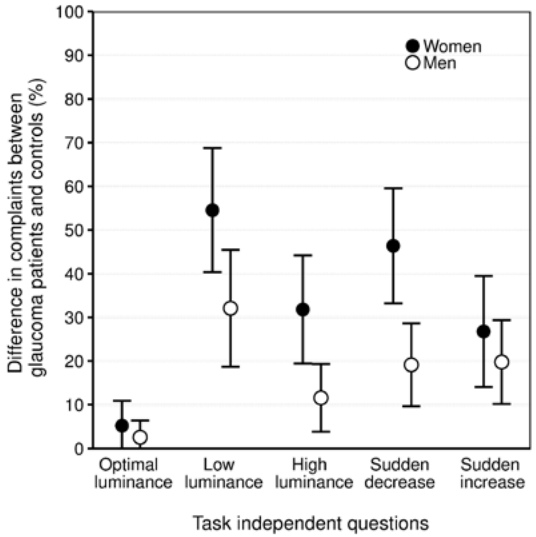

Figure 2. *Differences in complaints between glaucoma patients and controls for the five selected task-independent questions, stratified by gender. Error bars denote 95% confidence intervals.*

*Table 2. 2x2 tables showing the answers of the glaucoma patients to the task-independent questions (marked with a * in Table 1) for the four extreme luminance conditions.*

		High luminance		
		No Complaints	Complaints	Phi
Low luminance	No complaints	58	4	0.40
	Complaints	35	23	
		Sudden decrease		
		No Complaints	Complaints	Phi
Low luminance	No complaints	54	6	0.46
	Complaints	28	31	
		Sudden increase		
		No Complaints	Complaints	Phi
Low luminance	No complaints	55	5	0.40
	Complaints	33	25	
		Sudden decrease		
		No Complaints	Complaints	Phi
High luminance	No complaints	79	20	0.50
	Complaints	7	22	
		Sudden increase		
		No Complaints	Complaints	Phi
High luminance	No complaints	88	11	0.61
	Complaints	7	21	
		Sudden increase		
		No Complaints	Complaints	Phi
Sudden decrease	No complaints	82	6	0.62
	Complaints	15	27	

DISCUSSION

Differences in visual complaints between glaucoma patients and controls are small with optimal luminance but quite pronounced under extreme luminance conditions. The low luminance condition discriminates best, and complaints are more frequent with increasing disease severity.

Earlier vision-specific questionnaires included some questions related to light, dark, or adaptation, but did not analyze them separately (e.g., Mangione et al. (2001)24). Studies that used questionnaires with light, dark, or adaptation subscales revealed that glaucoma patients do indicate that they experience difficulty under extreme luminance conditions, which is in agreement with our findings.[25–28] One study showed an association with the severity of the visual field and the answers to a question on dark adaptation.[29] Other studies reported frequencies of complaints in patients, without comparing with controls. Hu et al. (2014) found, in glaucoma patients, complaint frequencies of 57% for the low and 42% for the high luminance condition.[2] We found 48% for the question 'Seeing outside at night when there is no moonlight' and 22% for the question 'Seeing outside on a sunny day'. Nelson, Aspinall & O'Brien (1999) found that 54% of glaucoma patients complained about adaptation to different levels of lighting.[6] Janz et al. (2001-1) researched symptoms in newly diagnosed glaucoma patients and found complaint frequencies of 30, 42, and 41% for the low, high, and decreasing luminance condition, respectively.[3] Lee et al. (1998) found high complaint frequencies for the low (82%) and high (46%) luminance condition.[5] They also included controls and found that complaints regarding the low and high luminance condition discriminated best between patients and controls, compared to other (non-luminance-specific) symptoms. Tatemichi et al. (2012), who used the same questions as Lee et al. but focussed on normal tension glaucoma patients, found somewhat lower complaint frequencies for the low (50%) and high (12%) luminance condition.[7] Again, the low luminance condition discriminated best between patients and controls. To summarize, the general message from these studies and our data is that a large percentage of glaucoma patients report difficulties with their visual functioning under extreme luminance conditions. An exception seems to be a study by Iester & Zingirian (2002), in which glaucoma patient complaint frequencies of 10 and 14% were reported for the high and decreasing luminance condition, respectively.[30] None of the earlier studies reported complaint frequencies for the optimal and increasing luminance condition.

A limitation of this study is that the glaucoma patients and controls differed significantly regarding age and gender. This resulted from the fact that we invited primarily the spouses of the patients as controls. We invited the spouses because (1) they live under the same luminance conditions as the corresponding cases and (2) we assumed them to be of similar age. However, spouses may differ in age, and because glaucoma is an age-related disease, the elder of the two is more likely to be the glaucoma case. By using a weight factor we normalized the age distribution of the control group to the glaucoma group. There were more women in the control group (because the elder of the two is more likely to be the male) than in the group of glaucoma patients and women reported more complaints than men, a finding that is consistent with other studies reporting that women generally have a more pronounced illness perception

than men.[3,31,32] The gender imbalance might have resulted in an underestimation of the observed luminance-specific differences. Another limitation is that the cases knew their diagnosis, and the controls presumably presumed that they were healthy. This limitation is not specific to our study; it will affect any case-control study with a questionnaire or other subjective test involved. Patients may exaggerate their impairments or they may become used to them. The latter option seems to be more common in glaucoma, but we can only speculate if that is also the case for luminance-specific impairments. Importantly, (1) the percentages of complaints were very low for questions that addressed the optimal luminance condition and (2) we found a clear dose-response relationship for the extreme luminance conditions. Both findings indicate the existence of some real luminance-specific effects. We did not screen for the presence of other eye diseases but rather assumed that they would be equally distributed amongst the groups. In this way we aimed for a realistic sample of elderly rather than super normals. Generally, missing values were more frequent in glaucoma patients than in controls (last column of Table 1). If we assume that this is due to mixing up 'Stopped doing this because of my eyesight' and 'Not applicable' by the patients, then the differences between glaucoma patients and controls have been underestimated (we considered 'Not applicable' as missing values during analysis). The high percentages of missing values for driving-related questions suggest that this mixing up is indeed the case. Strengths of our study are the sample size, the inclusion of questions regarding all five different luminance conditions, and the presence of a control group.

Currently, the primary functional test in glaucoma, perimetry, is performed at a comfortable, moderate background luminance of 10 cd/m^2. Our results suggest that a much better discrimination between glaucoma and healthy might be obtained by performing this test at a lower background luminance. Performing perimetry in glaucoma patients and controls over a wide range of luminances could be a good starting point for future research; earlier studies addressing perimetry as a function of luminance included healthy subjects only.[33–35]

Reported complaint frequencies in response to the question ´Seeing outside at night when there is no moonlight´ correspond to a sensitivity of 48% at a specificity of 94%, and a sensitivity of 33 and 74% for early and moderate/severe glaucoma, respectively. This suggests some potential for questionnaires in the field of glaucoma screening. Obviously, this potential has to be confirmed in other studies, especially in studies where the cases are not aware of their diagnosis. Screening with questionnaires may be interesting for research purpose, for example for case finding in huge cohort studies, where a full eye exam in all participants is not easily realized.[36]

In conclusion, the common view of glaucoma as a disease that is asymptomatic, especially in an early stage, appears only valid with optimal luminance. Differences in visual complaints between glaucoma patients and controls are greater under extreme luminance conditions, especially in the dark. This offers opportunities for better diagnostic tests and may be even screening. As the complaints impact vision already in an early disease stage, this study indirectly supports a timely detection and treatment of glaucoma.

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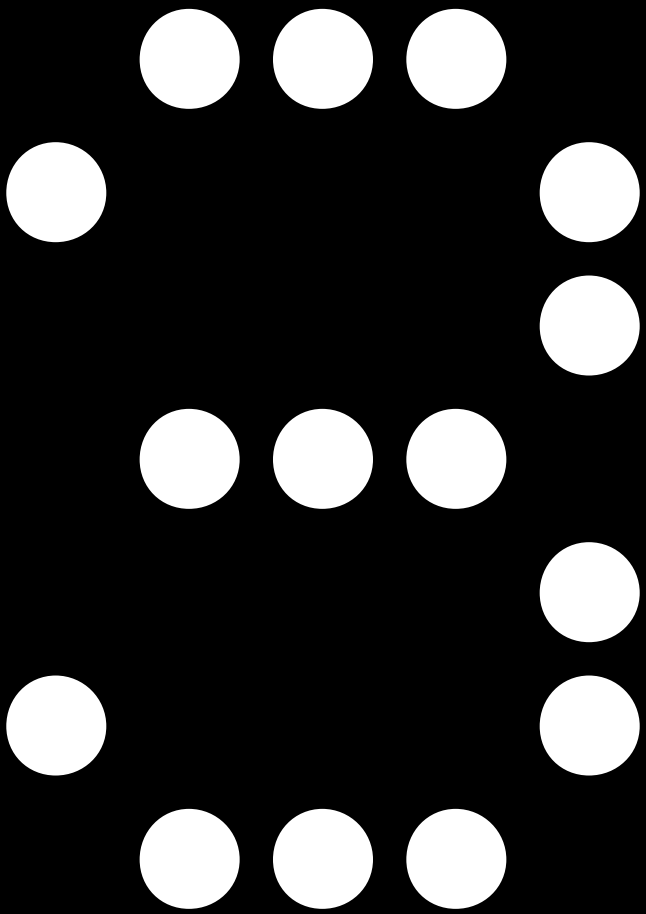

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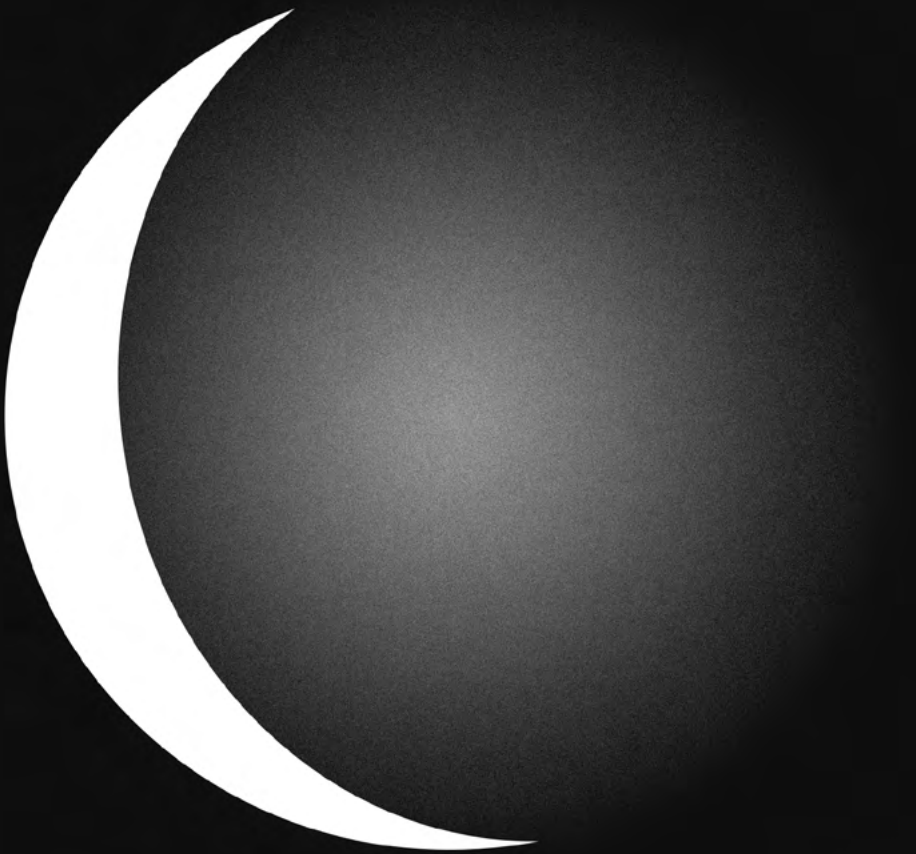

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VISUAL PERFORMANCE AS A FUNCTION OF LUMINANCE IN GLAUCOMA: THE DE VRIES–ROSE, WEBER'S, AND FERRY–PORTER'S LAW

ABSTRACT

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: 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 degree) as a function of luminance (0.02 to 200 cd/m^2). ANOVA was used to analyse the effect of glaucoma and luminance on CS and CFF; analyses were adjusted for age and gender.

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 to controls (P<0.001), with a smaller slope of the CFF versus log luminance curve, for both the fovea (6.8 versus 8.7 Hz/log unit; P<0.001) and the periphery (2.5 versus 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.

INTRODUCTION

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.

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.

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 primary open angle glaucoma 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 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,[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 out 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) 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., 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: two minutes for every log unit decrease;[27,28] one 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 an impaired pupil dilation at lower luminances, an 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^o 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 eyepatch. After two 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) with a maximum luminance of 470 cd/m^2 and a size of 40 by 34^o at the applied testing distance of 0.5 m, driven by the Psychophysics Toolbox (PTB-3; Brainard, 1997; Pelli, 1997) with Octave (version 3.2.4; www.gnu.org/software/octave/) for Linux (Ubuntu 10.10). 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.[32] The fixation target consisted of four thin lines with a length of 2^o, starting at 1^o 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)[33] 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 standard deviation (SD) between brackets. To avoid the inclusion of false-positive measurements ('happy trigger'), the logCS corresponding to a specific datapoint 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).[34] 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 two 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).

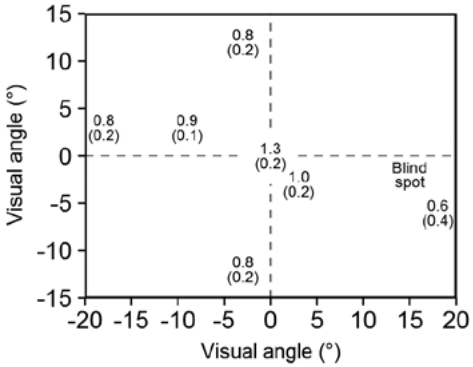

Figure 1. *Static perimetry test location grid (in right eye format) with corresponding mean logCS as determined in our healthy subjects at 130 cd/m², with standard deviation between brackets.*

Foveal and peripheral CFF were determined using an astable multivibrator circuit attached to a green LED (LL-504PGC2V-G5-2CD; peak wavelength 525 nm). 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/m². 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 test; proportions with a Chi-square test with Yates correction.

Glaucoma patients and controls appeared to differ regarding age. To enable a meaningful graphical 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, gender, 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 gender 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.[35] We adjusted the calculated pupil area for age and the Stiles-Crawford effect (1972),[36] assuming a Stiles-Crawford coefficient of 0.12.[37] 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.[38–40] We compared foveal and peripheral logCS and CFF as a function of luminance with those as a function of retinal illuminance.

RESULTS

Table 1 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 gender. 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.

Table 1. Characteristics of the study population.

	Cases (n=19)	Controls (n=45)	P value
Age (year; median [minimum, IQR, maximum])	71 (45, 64 to 73, 82)	54 (40, 47 to 65, 70)	<0.001
Gender, 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

IQR = interquartile range; * = 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); NA = not applicable.

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. 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 to 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 non-blind peripheral visual field, and in the best-preserved peripheral test location (all P<0.001), compared to 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 non-blind 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 non-blind 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 to 1.3 cd/m^2), the slope of the curve of the non-blind 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.

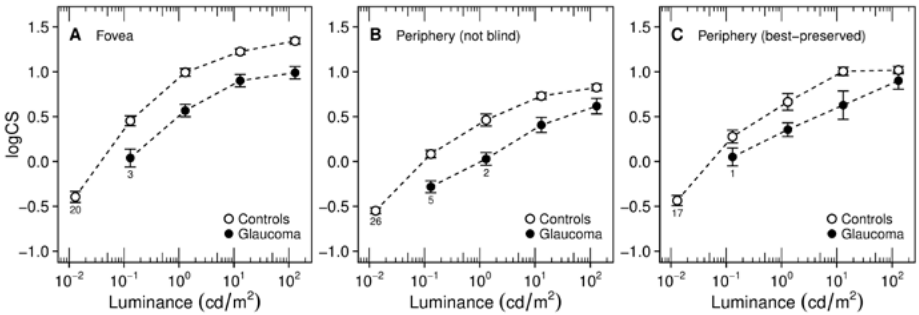

Figure 2. Perimetry as a function of luminance for glaucoma patients (filled circles) and controls (open circles). A: central contrast sensitivity; B: contrast sensitivity of the non-blind parts of the peripheral visual field; C: contrast sensitivity of the best-preserved part of the peripheral visual field (test location [+3,-3]). Error bars denote +/- 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.

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 to 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 to 7.4] Hz per log unit) was smaller than the slope of the controls (8.7 [8.0 to 9.4]), resulting in a more pronounced CFF difference towards higher luminances ($P<0.001$). A similar difference was found for the peripheral CFF (slope 2.5 [1.9 to 3.1] and 3.4 [2.6 to 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.

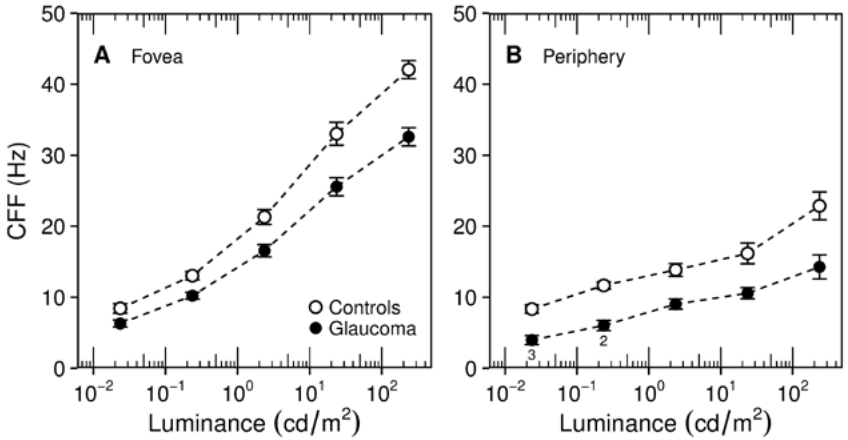

Figure 3. Critical flicker frequency as a function of luminance for glaucoma patients (filled circles) and controls (open circles). A: central CFF; B: peripheral CFF at 20° nasally. Error bars denote +/- 1 standard error. If applicable, individual data points were marked with the number of subjects who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

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 downwards compared to 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.

The static perimetry results of our study can be compared to four earlier studies in healthy subjects and one study including glaucoma patients. Our main contribution is a much wider luminance range. Aulhorn and Harms studied the influence of luminance on static perimetry in 10 healthy subjects.[41] They found a small decrease in retinal sensitivity going from 100 to 10 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 focussed on static perimetry at different luminances in healthy subjects.[42–44] 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.[45] 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 to 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 to 9.4]).[46–49] 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.[50,51] One study found that the slope did not depend on eccentricity,[49] which might be explained by the size of the illuminated background (whole retina for Lythgoe and Tansley,[49] 10° for Hecht and Verrijp,[50] and no illuminated background for Brooke[51] and our study). Several studies focussed 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.[52–54] 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.[55–57] The study of Essock 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.[58]

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, since 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. 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.[27] Mote and Riopelle studied the time course of foveal dark adaptation, for a series of preexposure luminances and durations. For a 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 one 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.[59] The relative contribution of rods and cones depends on many factors, and cannot easily be determined in the mesopic range.[60] In any case, since 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.[32] However, it turned out that, in damaged areas, the sensitivity was often unrecordable as soon as the luminance was reduced. For that reason, we focussed on the apparently intact areas. Since 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 versus 12 degree). 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 degree 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).[61–63] 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).[64] 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[65–67] and luminance,[68] and to differ between glaucoma patients and controls, at least at the default luminance used in perimetry.[45,69,70] 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.[69] 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.[71]

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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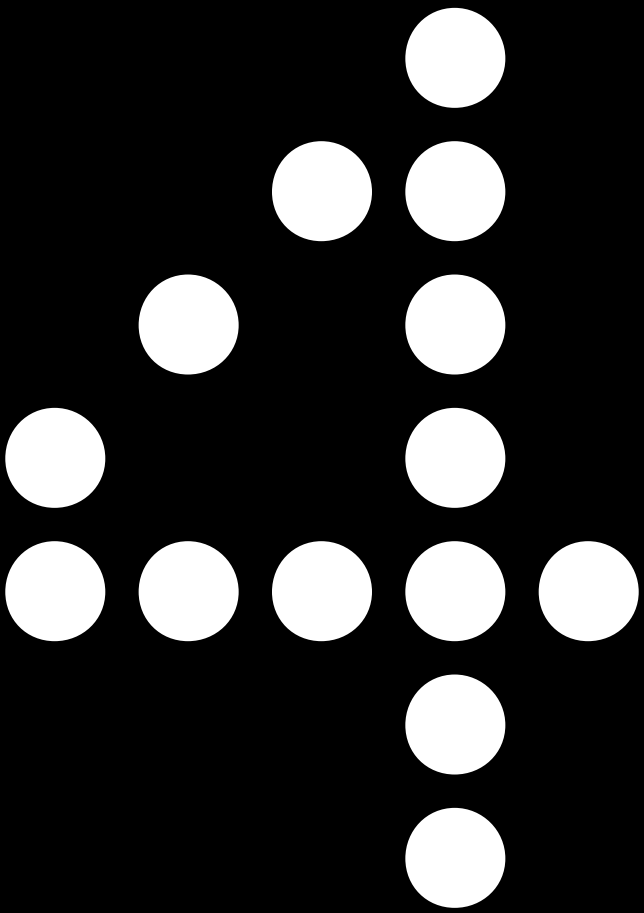

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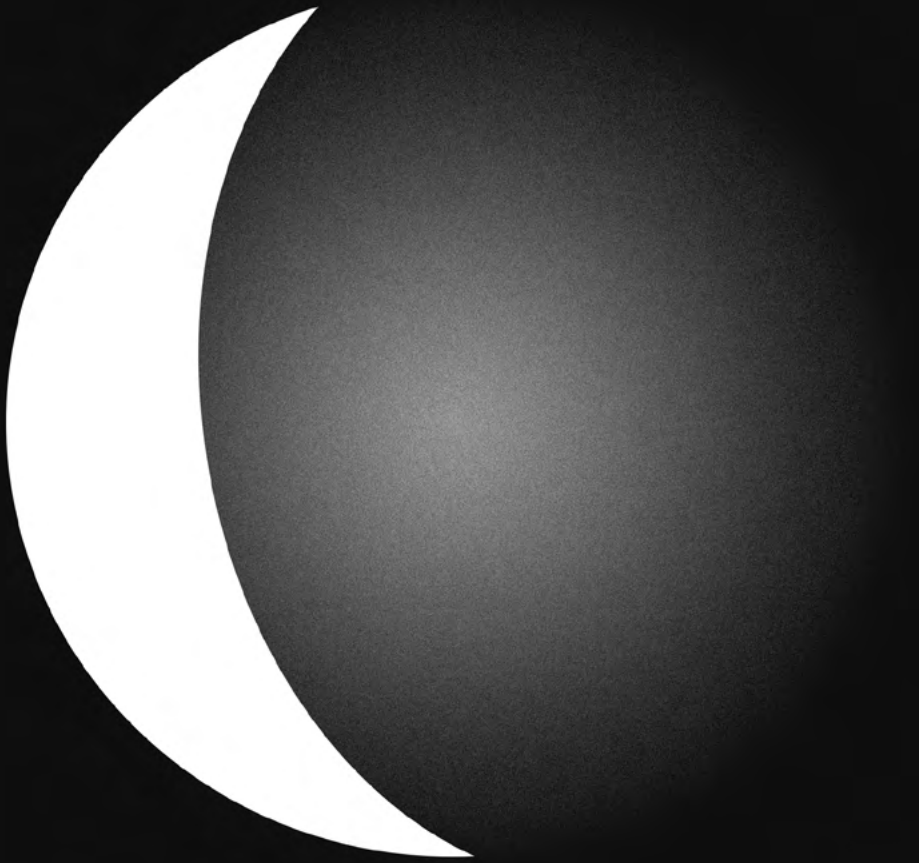

Submitted

SPATIAL CONTRAST SENSITIVITY FROM STAR- TO SUNLIGHT IN HEALTHY SUBJECTS AND PATIENTS WITH GLAUCOMA

ABSTRACT

Purpose: Glaucoma is often considered an asymptomatic disease but questionnaire studies suggest that this is only the case at appropriate luminance. We aimed (1) to determine whether Weber's law also holds under extremely high luminance conditions, and (2) to compare contrast sensitivity (CS) as a function of spatial frequency and luminance between glaucoma patients and healthy subjects.

Methods: Case-control study with 22 glaucoma patients and 51 controls, all with normal visual acuity. 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 8,500 cd/m^2, covering essentially the entire luminance range that can be experienced by a visual system on earth. ANOVA was used to analyze the effect of glaucoma and luminance on logCS; analyses were adjusted for age and gender.

Results: 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 curve did not differ between patients and controls for 1 and 10 cpd. For 3 cpd, patients had a lower CS than controls (approximately 0.2 log unit; P=0.017) and the difference was more pronounced at lower luminances (P<0.001).

Conclusions: We described visual function in healthy subjects and glaucoma patients over a wide range of luminances. Even in the apparent intact central visual field, visual performance is compromised in glaucoma over the entire luminance range, specifically for intermediate spatial frequencies.

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.[1] However, asymptomatic seems to be the case only at an appropriate luminance. Glaucoma patients, also those with early glaucoma, do complain regarding their visual performance under low, high, or changing luminance conditions.[2–8] These complaints suggest impaired dark and light adaptation, which seems strange. Although all cell types in the retina play a specific role in adaptation,[9] and subtle adaptation mechanisms may be affected in glaucoma,[10–13] the rods and cones rather than the RGCs are the primary site where the visual system adapts itself to ambient luminance. In recent studies, we measured light and dark adaptation in glaucoma patients and their visual performance at a steady low and average luminance, using standard automated perimetry.[14,15] 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 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),[16,17] and Weber's law (CS is constant at high luminances).[18] 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.[19] The transition to Weber's law corresponds to the decrease in quantum efficiency needed to keep up with higher luminances;[19] especially at the highest luminances, bleaching plays a role here.[20] 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.[21,22] 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.[22] 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.[23–33] Only one study, with only one subject, extended the measurements towards the higher luminances.[34] 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,[35–41] or only for higher spatial frequencies.[41–44] Others reported a normal CS in glaucoma patients.[44–49] 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 aim of this study was (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 essentially the entire luminance range that can be experienced by a visual system on earth (10^{-2} to 10^{4} cd/m^2).

METHODS

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.[50] 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.

Controls 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 controls 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,[51] 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.

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 meter, resulting in a stimulus size of 8 by 5 degrees (surrounding area 25x20 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.[52,53] Contrast was defined as Michelson contrast ($[L_{max}-L_{min}]/[L_{max}+L_{min}]$, 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. 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.[54] The CS was the reciprocal of this contrast threshold, that is, logCS = -log (contrast threshold). If the variability in the reversals exceeded the 97.5th percentile of the variability in the controls, the observation was excluded from the analysis. 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 8,500 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. 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 above 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^o 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 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. From the pupil diameter at these two luminances, we calculated the pupil diameter at other luminances (see below).

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 controls 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 healthy subjects (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).

Glaucoma patients and controls differed regarding age. To enable a meaningful graphical 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 age-weighted control group was only used in the graphs with both glaucoma patients and controls (Figs. 2 and 3); Figure 1 presents the original data.

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.[55] We adjusted the calculated pupil area for the Stiles-Crawford effect,[56,57] assuming a Stiles-Crawford coefficient of 0.12.[58] The Stiles-Crawford effect is a directional sensitivity of the retina that reduces the effective pupil diameter for cones (see Discussion section for a discussion regarding the relative contribution of cones and rods in our experiments).

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

RESULTS

Table 1 shows the general characteristics of the study population. The glaucoma patients were older than the controls; glaucoma patients and controls did not differ regarding gender. 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.

Table 1. Characteristics of the study population.

	Cases (n=22)	Controls (n=51)	P value
Age (year; median [IQR])	68 (60 to 73)	58 (49 to 66)	0.001
Gender, female, n (%)	8 (36%)	27 (53%)	0.30
Pupil diameter at 1 cd/m^2 (mm; median [IQR])	4.3 (3.4 to 5.1)	5.3 (4.7 to 5.8)	0.001*
Pupil diameter at 450 cd/m^2 (mm; median [IQR])	3.1 (2.5 to 3.4)	3.0 (2.7 to 3.4)	0.84†
Visual acuity (logMAR; median [IQR])	0.00 (-0.08 to 0.00)	-0.08 (-0.08 to 0.00)	0.002‡
HFA MD (dB; median [IQR])	-13.5 (-16.8 to -10.5)	NA	NA

IQR = interquartile range; MD = mean deviation; NA = not applicable; * = with age-adjusted control group P value 0.008 (corresponding median 5.3 mm); † = with age-adjusted control group P value 0.65 (corresponding median 3.1 mm); ‡ = with age-adjusted control group P value 0.039 (corresponding median -0.08).

Figure 1 presents the CS as a function of luminance (Fig. 1A), and retinal illuminance (Fig. 1B) of the controls. 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.

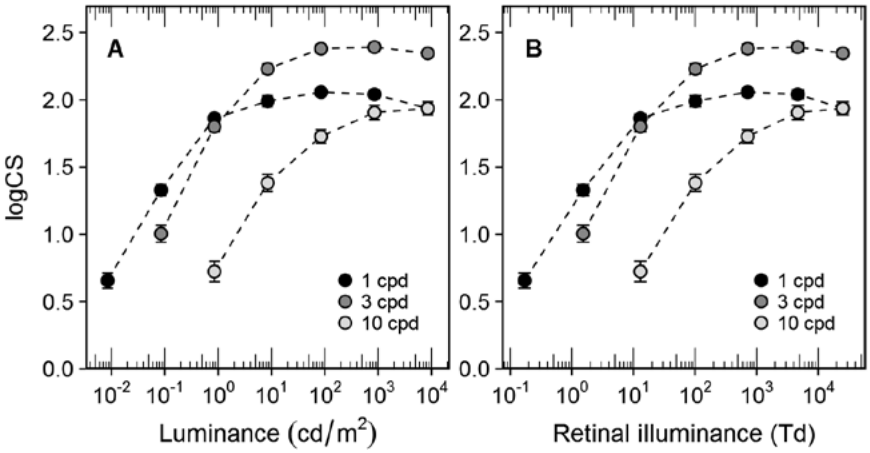

Figure 1. *Spatial contrast sensitivity as a function of luminance (A) and retinal illuminance (B) of controls. Error bars (often smaller than the data points itself) denote +/- 1 standard error. LogCS decreased significantly at the highest luminance for 1 cpd (P=0.003). The corresponding pupil diameters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

Figure 2 presents the CS as a function of luminance (Fig. 2A-C) and retinal illuminance (Fig. 2D-F), for glaucoma patients and age-weighted controls. The slopes (95% confidence interval) belonging to the De Vries-Rose law were 0.73 (0.47 to 0.99) and 0.74 (0.51 to 0.96) for 1 cpd, 0.77 (0.51 to 1.03) and 0.87 (0.63 to 1.11) for 3 cpd, and 0.67 (0.40 to 0.95) and 0.60 (0.30 to 0.90) for 10 cpd, for glaucoma patients and controls, respectively (expected slope 0.5; see Discussion section).

Obviously, luminance had an effect on the logCS for each spatial frequency (P<0.001). For 1 cpd, the logCS did not differ between glaucoma patients and controls (P=0.19). The effect of glaucoma was not independent of luminance (significant interaction between glaucoma and luminance; P=0.002), presumably due to the divergence between the groups at 0.85 cd/m^2. For 3 cpd, glaucoma patients had a lower logCS compared to controls (P=0.017); the difference between both groups was more pronounced for the lower luminances (significant interaction between glaucoma and luminance; P<0.001). For 10 cpd, the logCS did not differ between glaucoma patients and controls (P=0.22), and this was independent of luminance (no significant interaction between glaucoma and luminance; P=0.09).

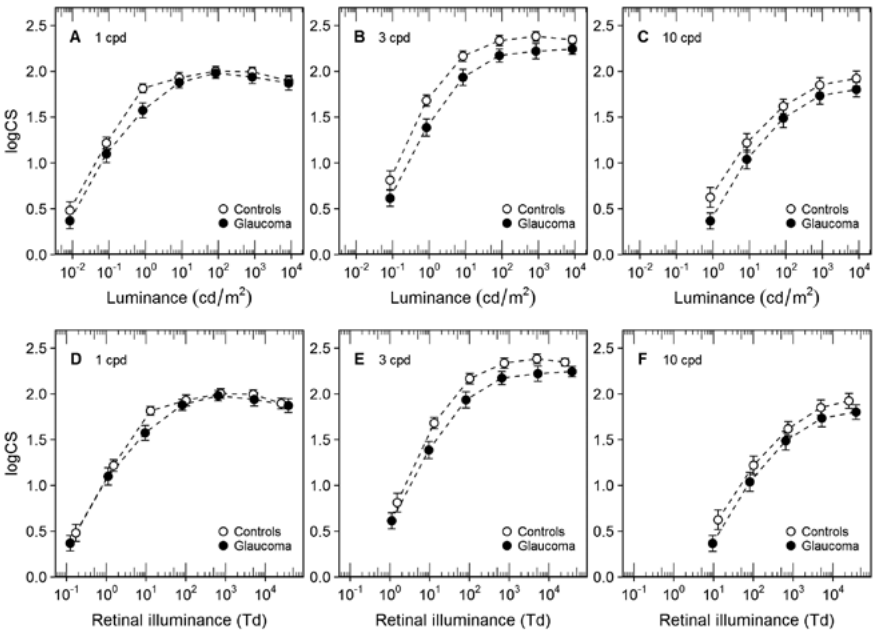

Figure 2. *Spatial contrast sensitivity as a function of luminance (A, B, and C) and retinal illuminance (D, E and F) for glaucoma patients and age-weighted controls. Error bars denote +/- 1 standard error. The corresponding pupil diameters were 2.5, 3.0, 3.4, 3.9, 4.3, 4.8, and 5.2 mm for the glaucoma patients and 2.0, 2.9, 3.7, 4.5, 5.4, 6.2, and 7.0 mm for the controls.*

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 background luminance curve of glaucoma patients is similar to those of healthy subjects for 1 and 10 cpd. For 3 cpd, glaucoma patients have a lower CS than healthy subjects; the difference seems more pronounced at lower luminances.

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.[29,33,59] 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-Perez and Peli,[60] 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 (typically 10,000 cd/m^2).[24–26,30–32] 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.[23,27–29,33,61] A possible

explanation for the discrepancy around 100 cd/m^2 could be 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.[34] 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.[62] 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 to 0.96), 0.87 (0.63 to 1.11), and 0.60 (0.30 to 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.[63]

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 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, which is in agreement with our findings. The typical band-path pattern of the abnormalities we found (more abnormalities at intermediate frequencies than at low and high frequencies), was not reported in these studies. A possible explanation for this discrepancy is that we required a strictly normal visual acuity. Also, many studies employed a lower (6 - 8 cpd) 'high' spatial frequency than we did whereas others used a higher spatial frequency, more close to the spatial resolution of the eye (12 - 30 cpd). Using the same method as we did, Junoy Montolio et al. measured CS for two spatial frequencies at 150 cd/m^2.[13] They found a decrease in CS in glaucoma patients of 0.2 log unit at 1 cpd (we found 0.02 log unit), and of 0.3 log units at 4 cpd (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 indicates that involvement of low spatial frequencies is restricted to advanced disease. Stimulus size may also play a role.[64] Anyhow, if CS is to be tested in glaucoma and time is restricted, an intermediate spatial frequency seems a safe choice. 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 (3 cpd).[65] Glaucoma patients had a lower CS, at both luminances, which is in agreement with our results. We found a noteworthy difference of 0.2 log units between glaucoma patients and controls for 1 cpd at 0.85 cd/m^2. As described above, there are no studies available to confirm this striking difference at this high-mesopic luminance level.[58]

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 lux)	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.

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.[66] 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.[67]

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 order to be able to predict the pupil diameter at other luminances (see Methods section). 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 camera. 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 Methods section). Although this approach has been published already a long time ago,[56] 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.[29,31,33]

In this study, there was a difference in age distribution between glaucoma patients and controls. Still, the groups showed considerable overlap, and all statistical analyses and graphs were adjusted for age. 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 essentially all luminances that can be experienced on earth. The lowest luminance is typically at the lower end of the luminance range that can be found outdoor in the public space after dark;[68] 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.[34]

Our main finding is a lower CS at 3 cpd in glaucoma, which is more pronounced at lower luminances but present over the entire luminance range. No differences were found at 1 and 10 cpd (except for 1 cpd at 1 cd/m^2). At first sight, this suggests a limited impact on glaucoma patients' daily life. However, exactly the intermediate spatial frequencies are pivotal for the detection of edges.[53,69] Edges (or contours) are, unlike sine-wave patterns, very common features of natural images. For that reason, a selective loss of intermediate spatial frequencies may indeed have a relevant impact. As

mentioned in the Introduction section, glaucoma patients are mainly asymptomatic in case of appropriate illumination. This is in agreement with the significant interaction we found in the ANOVA for glaucoma and luminance at 3 cpd ($P<0.001$), but can be understood better from Figure 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). In a previous study,[15] 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.[64]

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.[22] This can be seen in Figure 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. Figure 3 shows the difference in logCS between 3 and 1 cpd as a function of luminance, for glaucoma patients and age-matched 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.[13]

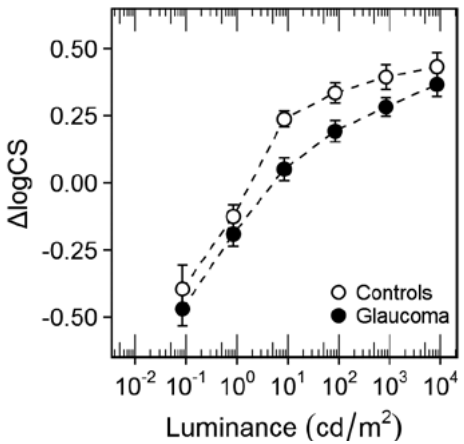

Figure 3. *Difference in logCS between 3 and 1 cpd as a function of luminance, for glaucoma patients and age-weighted controls. Error bars denote +/- 1 standard error.*

In conclusion, we described visual function in healthy subjects and glaucoma patients over a wide range of luminances. Even in the apparent intact central visual field, visual performance is worse in glaucoma patients than in healthy subjects over the entire luminance range, specifically for intermediate spatial frequencies. As mentioned in the Introduction section, 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. 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.

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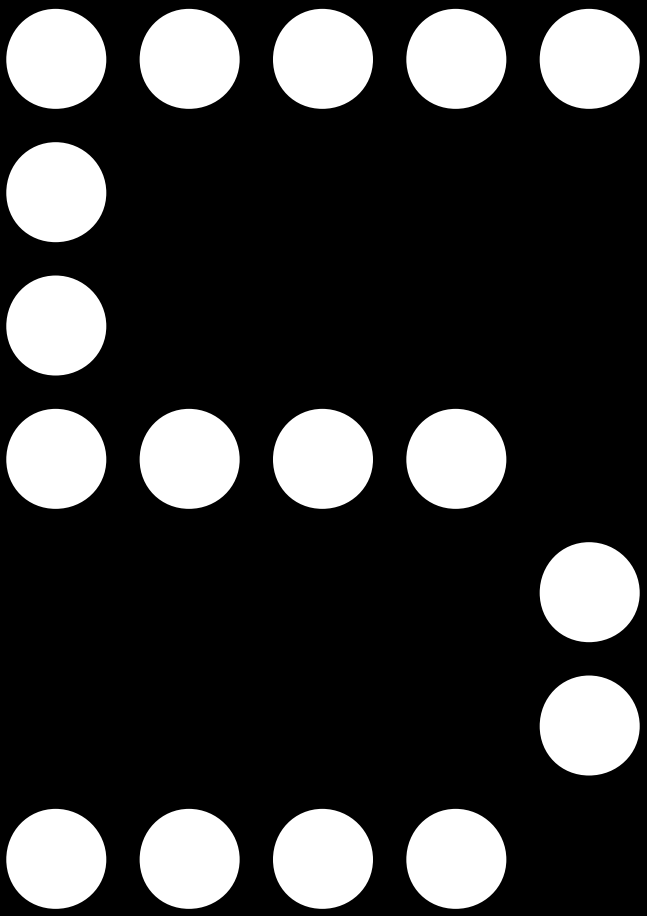

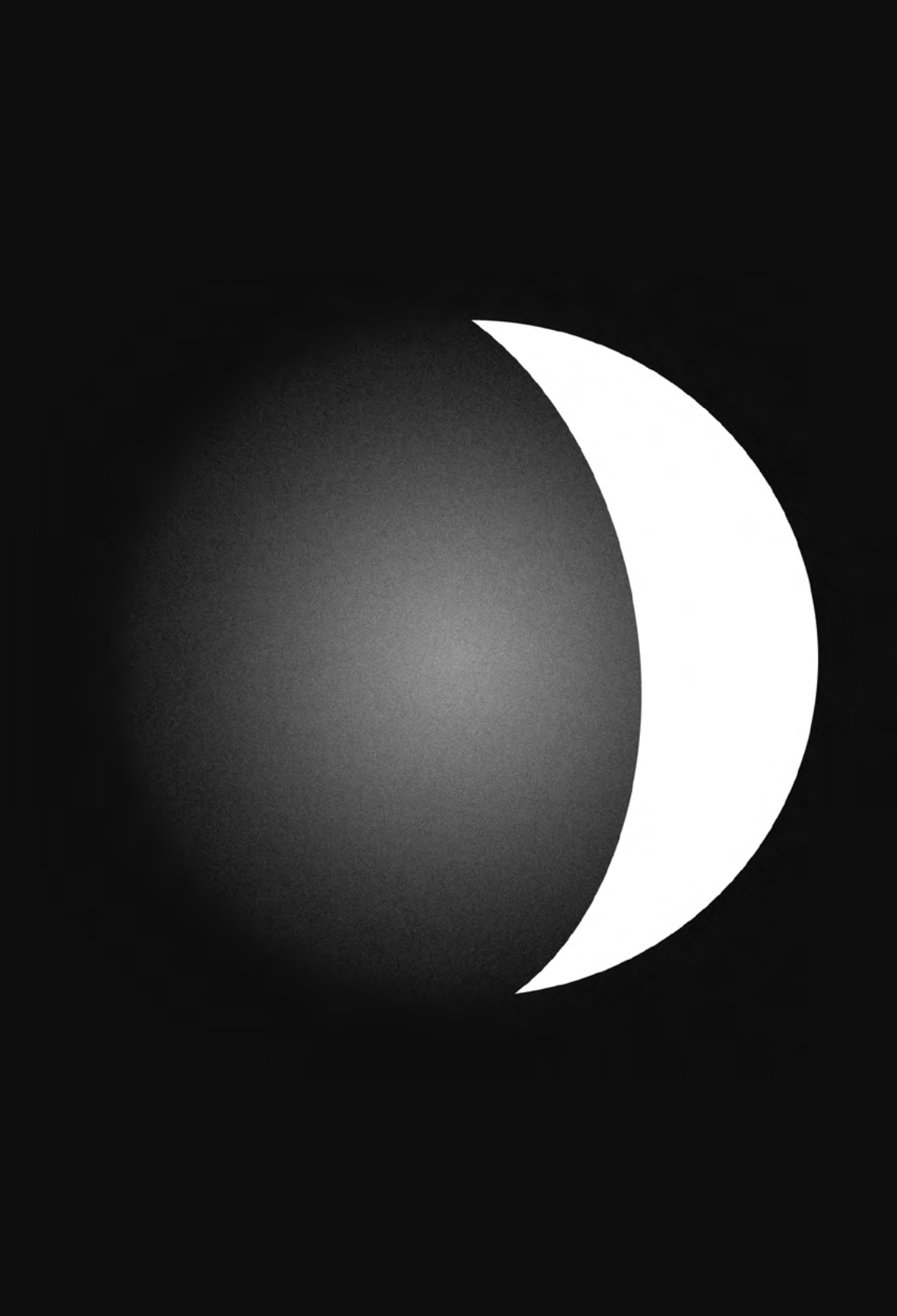

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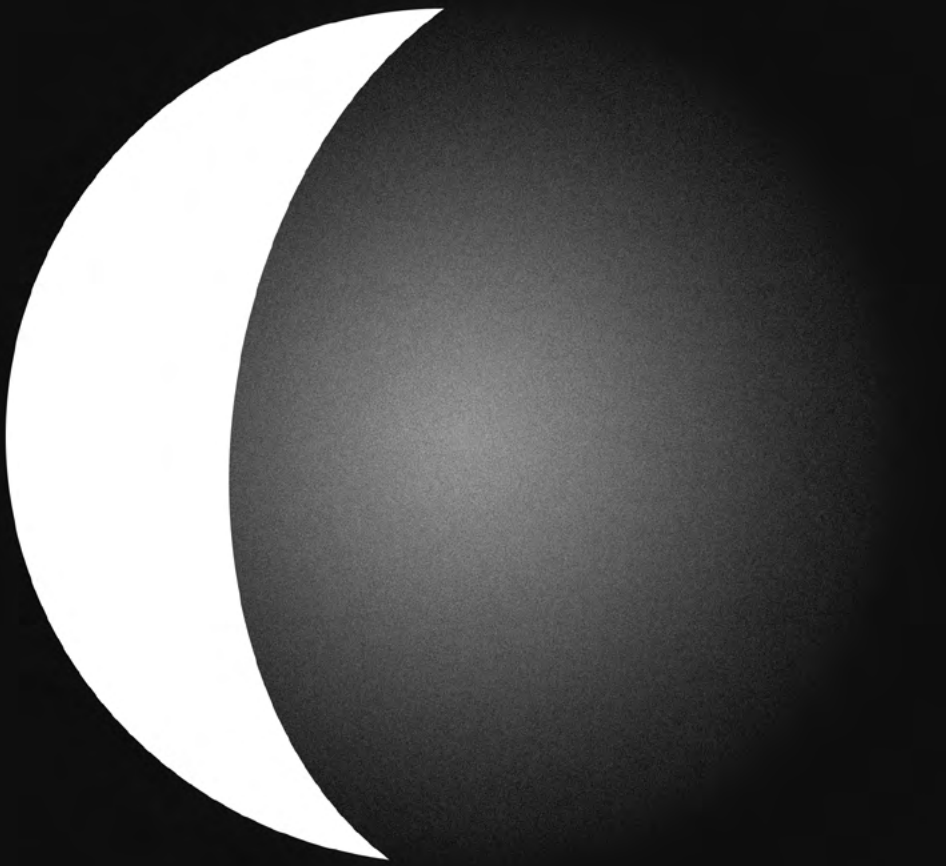

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FOVEAL LIGHT AND DARK ADAPTATION IN PATIENTS WITH GLAUCOMA AND HEALTHY SUBJECTS: A CASE-CONTROL STUDY

ABSTRACT

Purpose: To determine whether foveal light and dark adaptation are affected in glaucoma.

Methods: Case-control study with 23 glaucoma patients and 51 controls. Light and dark adaptation were measured twice. After 10 minutes pre-adaptation to 0.0032 cd/m^2, the background luminance increased stepwise to 320 (5 log unit step) or 10,000 cd/m^2 (6.5 log unit step) for 10 minutes, then it decreased back to 0.0032 cd/m^2 for 30 minutes. Foveal contrast sensitivity [CS]) as a function of time was determined using a 1.15 degree increment. Time resolution of the experiments was 30 seconds. Multiple linear regression was used to analyse the effect of glaucoma on the CS plateau and adaptation time (time to reach the plateau minus 3 dB); analyses were adjusted for age and gender.

Results: After light adaptation to 320 and 10,000 cd/m^2, glaucoma patients had a 0.22 ($P<0.001$) and 0.13 ($P=0.010$) log unit lower CS plateau than controls, respectively. After dark adaptation, this difference was 0.21 ($P=0.018$) and 0.30 ($P<0.001$) log unit, respectively. Light adaptation occurred too fast to determine an accurate light adaptation time. Dark adaptation times of glaucoma patients and controls were similar, for both the 5 (7.2 versus 5.5 minutes; $P=0.10$) and the 6.5 (18.2 versus 16.6 minutes; $P=0.14$) log unit step.

Conclusions: After a sudden increase or decrease in luminance, the logCS adaptation curves of glaucoma patients are shifted downwards compared to the curves of healthy subjects. Glaucoma patients have a lower CS plateau than healthy subjects, for both light and dark adaptation; dark adaptation times are similar.

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.[1] However, asymptomatic seems to be the case only at appropriate luminance. Glaucoma patients, also those with early glaucoma, do complain regarding their visual performance under low, high, or changing luminance conditions.[2–8] So far, visual performance under changing luminance conditions is a largely unaddressed topic in glaucoma.

The most straightforward approach in exploring visual performance under changing luminance conditions is the measurement of the classical dark adaptation curve. Even though the rods and cones rather than the RGCs are the primary site where the visual system adapts itself to ambient luminance,[9] impaired dark adaptation in glaucoma has been reported. The first studies that measured dark adaptation in glaucoma patients found a delayed curve for the central part[10–12] and the periphery[13] of the visual field. Variability, however, resulted in a poor diagnostic performance.[14] Others did not find clear differences in dark adaptation time between glaucoma patients and controls, neither for the peripheral visual field[15] nor for the central visual field,[16] at odds with the earlier studies. Given the clear complaints emerging from the questionnaire studies, we considered a new, detailed look at this issue pivotal. Moreover, studies that measured light adaptation in glaucoma patients are apparently completely lacking.

The aim of this study was to determine whether foveal light and dark adaptation are affected in glaucoma. For this purpose we performed a case-control study involving glaucoma patients and healthy controls, all with a normal visual acuity. Following a paradigm as used by Zihl and Kerkhoff in brain-damaged patients,[17] we measured Weber contrast sensitivity (CS) using a 1 degree diameter increment in the central visual field, after a stepwise increase or decrease in background luminance. We employed two step sizes, corresponding to respectively a dark environment versus a well-illuminated indoor setting and a dark environment versus outdoor at noon on a sunny day.

MATERIALS AND METHODS

Study population

In this prospective case-control study we included 23 glaucoma patients (cases) and two groups of 51 and 52 healthy subjects, respectively (controls). 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 visitors of the outpatient department of the department of Ophthalmology, University Medical Center Groningen, using the visual field database of the Groningen Longitudinal Glaucoma Study (GLGS). The GLGS is an observational cohort study performed in a clinical setting.[18] The subpopulation selected for this study comprised primary open angle glaucoma 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 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 per control group. 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 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,[19] 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.

Data collection

Before the adaptation tests were performed, the pupil diameter was measured at two different luminances, being 2 and 320 cd/m^2. A circular stimulus with a diameter of 12^o was projected on a monitor (Radiforce G21; EIZO) 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 eyepatch. After two minutes, a picture of the eye was taken using 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.[20]

Adaptation was tested monocularly. We measured foveal contrast sensitivity during adaptation to a high luminance, after a previous adaptation to a low luminance (light adaptation), and during adaptation to a low luminance, after previous adaptation to a high luminance (dark adaptation). Before the experiment, the subjects received explanation in a dimly lit room; no additional bleaching was performed. Light and dark adaptation were measured twice, with a luminance step of 5 log units, and a luminance step of 6.5 log units. The group of glaucoma patients performed both step sizes, on a separate day; the two control groups performed each only one of the step sizes. For the 5 log units luminance step size, a high-luminance black and white monitor (Radiforce G21; EIZO; maximum luminance 470 cd/m^2) was used with a testing distance of 0.5 meter; for the 6.5 log units step size, a projector (P1387W; Acer; maximum luminance 16,000 cd/m^2, white light by driving the R, G, and B channel identically) positioned at the rear of a see-through PVC projection screen was used with a testing distance of 0.3 meter. This resulted in viewing angles of 44 degrees horizontally by 34 degrees vertically for the first setup, and 50 by 33 degrees for the second setup. The low-luminance condition was obtained by a 1 log unit decrease in luminance of the screen combined with absorptive neutral density (ND) filters with an optical density of 4 (transmission $1*10^{-4}$; #65-817 and #65-822, Edmund Optics) for the 5 log unit step, and of 5.5 (transmission $1*10^{-5.5}$; #65-817, #65-819, and #65-822, Edmund Optics) for the 6.5 log unit step. During the test, the patient's head rested in a chin-rest to maintain the testing distance. Both setups were driven by the Psychophysics Toolbox (PTB-3; Brainard, 1997; Pelli, 1997) with Octave (version 3.2.4; www.gnu.org/software/octave/) for Linux (Ubuntu 10.10).

In both experiments, the test started with a 10 minute adaptation to the low-luminance condition, with a background luminance of 0.0032 cd/m^2. After that, the background luminance increased stepwise to the high-luminance condition, with a background luminance of 320 (5 log unit step) or 10,000 cd/m^2 (6.5 log unit step). Starting directly after the change in luminance, the foveal light detection threshold was determined every 30 seconds, for 10 minutes in total (light adaptation). Hereafter, the background luminance decreased stepwise back to 0.0032 cd/m^2. Again, the foveal light detection threshold was determined every 30 seconds, for 20 minutes after the 5 log unit step and 30 minutes after the 6.5 log units step (dark adaptation). The foveal light detection threshold was determined using an increment with a diameter of 1.15 degree and a duration of 500 ms.[17] A 4-2 dB staircase procedure was used to determine the threshold Weber contrast ($[L_{stimulus}-L_{background}]/[L_{background}]$); CS was the inverse of this threshold. The initial contrast was 0.0016. In between the stimuli there was a random interval with a mean (SD) duration of 1.6 (0.4) seconds. During each threshold determination, a fixation target surrounded the center of the screen. This fixation target consisted of four squares of 0.2° size, located at the horizontal and vertical meridian at 2° eccentricity. The experiments were performed with optimal correction for the viewing distance. As we were primarily interested in differences in overall visual function between glaucoma patients and healthy subjects, no cycloplegia, mydriasis, or artificial pupil was used. Measurements were preceded by a short familiarization trial. Luminance levels were measured with a Minolta luminance meter with built-in photometric filter (LS-110; Minolta Camera Co. Ltd., Japan).

Data analysis

The study population was described using nonparametric descriptive statistics (median with interquartile range [IQR]). Univariable comparisons between cases and controls were made with a Mann-Whitney test (continuous variables) or Chi-square test with Yates correction (proportions).

Especially in the beginning of the dark adaptation phase, subjects were not always able to see the stimulus, even not at the highest contrast that could be offered. The logCS at these time points was defined as -1.3 (0.2 less than the lowest logCS that could be measured). However, later on, after at least two time points at which the stimulus was seen, unseen stimuli were considered missing (excluded from analysis). To avoid the inclusion of false-positive responses, we also excluded logCS values that were higher than the controls' logCS plateau plus 2.6 standard deviations (Chauvenet's criterion).[21]

To compare foveal light and dark adaptation between glaucoma patients and controls, we plotted the CS as a function of time. Glaucoma patients and controls appeared to differ regarding age. To enable a meaningful graphical 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 age-weighted control group was only used in the graphs.

Per subject, we determined the CS plateau after light and dark adaptation by taking the median CS of the last four measurements in the high-luminance (after 8 minutes), and the low-luminance (after 18 and 28 minutes, for the 5 and 6.5 log unit luminance step, respectively) condition. We defined the 'adaptation time' by considering a moving time window consisting of four consecutive time points. As soon as the median logCS belonging to these four time points came within -3 dB from the CS plateau, we took as the adaptation time the time halfway the second and third time point. The CS plateaus and the adaptation times of the glaucoma patients and controls were compared using multiple linear regression, adjusted for age and gender. A P value of 0.05 or less was considered statistically significant.

RESULTS

Table 1 shows the general characteristics of the study population. The glaucoma patients were older than the controls; glaucoma patients and controls did not differ regarding gender. Most patients had moderate or severe glaucoma in the study eye, with a median (IQR) visual field MD of -13.7 (-18.6 to -10.8) dB.

Figure 1 presents logCS as a function of time for the glaucoma patients and controls, for the 5 (Fig. 1A) and 6.5 (Fig. 1B) log unit luminance step. For the 5 log unit luminance step, the mean (SD) CS plateau after light adaptation was at logCS = 1.41 (0.27) for the glaucoma patients and at 1.66 (0.24) for the controls. After dark adaptation this was -0.58 (0.41) and -0.29 (-0.34). The mean (SD) dark adaptation time was 7.2 (4.7) and 5.5 (3.4) minutes for the glaucoma patients and the controls, respectively. Because both the glaucoma patients and the controls already reached their light adaptation CS

plateau within the resolution of our sampling, a light adaptation time (see Methods section for definition) could not be determined. For the 6.5 log unit luminance step, the CS plateau after light adaptation was at logCS = 1.38 (0.23) for the glaucoma patients and at 1.55 (0.18) for the controls. After dark adaptation this was -0.63 (0.40) and -0.30 (0.30). The dark adaptation time was 18.2 (2.5) and 16.6 (4.5) minutes for the glaucoma patients and the controls, respectively.

Table 1. *Characteristics of the study population.*

	Cases (n=23)	**Controls** *5 log unit step* (n=51)	**P value**	**Controls** *6.5 log unit step* (n=52)	**P value**
Age (year; median [IQR])	69 (61 to 73)	57 (49 to 65)	<0.001	58 (49 to 66)	<0.001
Gender, female, n (%)	9 (39%)	26 (51%)	0.49	27 (52%)	0.44
Pupil diameter at 2 cd/m^2 (mm; median [IQR])	4.0 (3.0 to 4.7)	5.1 (4.5 to 5.5)	0.001*	5.3 (4.7 to 5.8)	<0.001†
Pupil diameter at 320 cd/m^2 (mm; median [IQR])	3.2 (2.5 to 3.7)	3.0 (2.8 to 3.3)	0.79‡	3.0 (2.7 to 3.4)	0.81§
Visual acuity (logMAR; median [IQR])	0.00 (-0.08 to 0.00)	-0.08 (-0.08 to 0.00)	0.001$^{\|\|}$	-0.08 (-0.08 to 0.00)	0.001$^{\#}$
Median (IQR) HFA MD (dB)	-13.7 (-18.6 to -10.8)	NA	NA	NA	NA

IQR = interquartile range; HFA MD = Humphrey Field Analyzer mean deviation; NA = not applicable; age-adjusted P values: * = 0.003 (median 4.9 mm); † = 0.002 (median 5.3 mm); ‡ = 0.59 (median 3.0); § = 0.98 (median 3.2 mm); || = 0.005 (median -0.08); # = 0.014 (median -0.06).

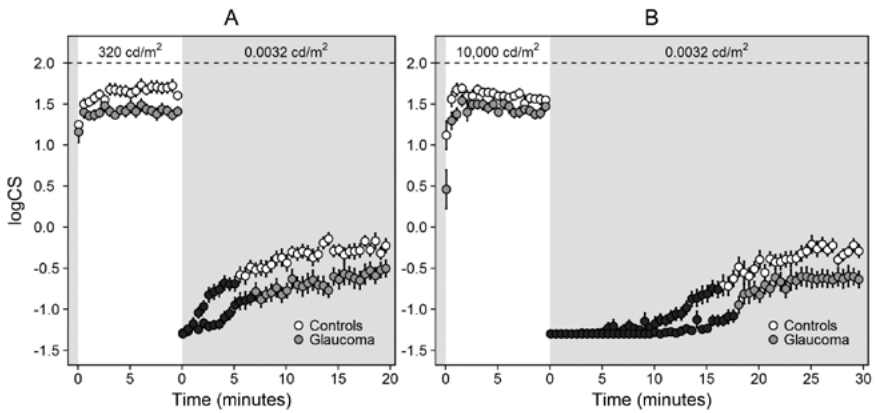

Figure 1. *Contrast sensitivity (logCS) as a function of time for glaucoma patients (gray data points) and controls (white data points), for the 5 (A) and 6.5 (B) log unit change in luminance. Both tests were preceded by a 10 minute adaptation to a background luminance of 0.0032 cd/m^2. The black data points correspond to a logCS more than 3 dB below the dark adaptation CS plateau (that is, the transition between the black and white/gray data points depicts the adaptation time). Error bars denote +/- 1 standard error.*

Table 2 presents the corresponding multivariable analysis. For both luminance step sizes, the CS plateau after light and dark adaptation was lower in the glaucoma patients than in the controls. Dark adaptation time did not differ between glaucoma patients and controls.

Table 2. *Multivariable regression analysis.*

		β	P value
5 log unit change in luminance (0.0032 versus 320 cd/m^2)			
Light adaptation CS plateau	Glaucoma*	-0.221	<0.001
	Age (years)	-0.010	<0.001
	Gender†	-0.130	0.020
Dark adaptation CS plateau	Glaucoma*	-0.214	0.018
	Age (years)	-0.015	0.005
	Gender†	-0.105	0.16
Dark adaptation time (minutes)	Glaucoma*	1.579	0.10
	Age (years)	0.121	0.006
	Gender†	1.091	0.17
6.5 log unit change in luminance (0.0032 versus 10,000 cd/m^2)			
Light adaptation CS plateau	Glaucoma*	-0.134	0.010
	Age (years)	-0.004	0.038
	Gender†	0.030	0.49
Dark adaptation CS plateau	Glaucoma*	-0.297	<0.001
	Age (years)	-0.013	<0.001
	Gender†	-0.194	0.005
Dark adaptation time (minutes)	Glaucoma*	1.690	0.14
	Age (years)	0.127	0.011
	Gender†	-0.065	0.95

CS = contrast sensitivity; β = regression coefficient; * = glaucoma vs. controls; † = women vs. men.

For the subgroup of healthy subjects, the logCS of the dark adaptation plateau was significantly associated with age (β = -0.010 log unit per year for 0.0032 from 320 cd/m^2 [P=0.024]; β = -0.009 log unit per year for 0.0032 from 10,000 cd/m^2 [P=0.013]). The logCS of the light adaptation plateau was significantly associated with age at 320 cd/m^2 (β = -0.009 log unit per year [P=0.007]) but not at 10,000 cd/m^2 (β = -0.003 log unit per year [P=0.27]). All these analyses were adjusted for gender.

For the subgroup of glaucoma patients, the logCS of the dark and light adaptation plateaus were nonsignificantly associated with the visual field MD (β = 0.017 log unit per dB for 0.0032 from 320 cd/m^2 [P=0.19]; β = 0.015 log unit per dB for 0.0032 from 10,000 cd/m^2 [P=0.23]; β = 0.010 log unit per dB for 320 cd/m^2 [P=0.33]; β = 0.009 log unit per dB for 10,000 cd/m^2 [P=0.33]). All these analyses were adjusted for age and gender.

DISCUSSION

After a sudden increase or decrease in luminance, the logCS adaptation curves of glaucoma patients are shifted downwards compared to the curves of healthy subjects. Glaucoma patients have a lower CS plateau than healthy subjects, for both light and dark adaptation; dark adaptation times are similar.

Adaptation depends highly on testing conditions such as the luminance and time of pre-adaptation, the luminance to which a subject adapts, and the stimulus size and eccentricity.[22–24] The methods we used in our study were inspired by the experiment of Zihl and Kerkhoff, performed in healthy subjects and patients with brain damage. They also used a 1.15 degree, 500 ms foveal increment and a similar time structure to measure light and dark adaptation.[17] In contrast to our study, they used an asymmetrical design in terms of luminance: a pre-adaptation to 3.2 cd/m^2, light adaptation to 320 cd/m^2, and dark adaptation to 0.00032 cd/m^2. We decided to make the luminance steps symmetrical, and thus made the pre-adaptation and dark adaptation luminance identical. The employed 0.0032 cd/m^2 corresponds roughly to a starry sky without moon and is typically at the lower end of the luminance range that can be found outdoor in the public space after dark.[25] We adopted their 320 cd/m^2 for light adaptation; we added a second experiment, with 10,000 cd/m^2. In this way we mimicked both a well-illuminated indoor setting and outdoor at noon on a sunny day. Zihl and Kerkhoff found that almost all light adaptation happened within 2 minutes. This is in agreement with our findings. Baker studied light adaptation to 185 and 1850 cd/m^2 from complete darkness (10 minutes), using a stimulus of 1 degree.[26] He found a similar pattern of light adaptation and – for 1850 cd/m^2 – also a small decrease in contrast sensitivity over time after approximately 3 minutes, similar to what we found for 10,000 cd/m^2 (Fig. 1B). Zihl and Kerkhoff reported a steady contrast sensitivity 12 minutes after a 6 log unit decrease in luminance. This accords with our adaptation times of 5.5 and 16.6 minutes after a 5 and 6.5 log unit decrease in luminance, respectively.

We did not find any study that measured light adaptation in glaucoma patients. Studies that measured dark adaptation in glaucoma patients mainly date back to the beginning of the previous century.[10–13,15,27,28] Generally, they found an impaired dark adaptation in glaucoma patients; differences in methodology, data reporting, case definition, and outcome measures inhibit a detailed quantitative comparison with our results. More recently, Jonas et al. studied dark adaptation in glaucoma patients with a normal visual acuity, using a Goldmann-Weekers dark adaptometer (Haag-Streit, Berne, Switzerland) with a central stimulus of 11 degrees. In agreement with our findings, they found curves in glaucoma patients and age-matched controls that had a similar shape but differed in plateau.[16] Panos et al. found differences in dark adaptation between congenital and late-onset glaucoma; a direct comparison to healthy subjects was not reported.[29]

We did not find a significant association between visual field MD and the logCS values of the dark and light adaptation plateaus. A possible explanation for this nonsignificance is the limited variability in MD in our patient group. However, all four β values were in the expected direction (positive, that is, a lower logCS with a more negative MD).

Interestingly, if we multiply the β values (ranging from 0.009 to 0.017 log unit per dB; Results section) with the median MD of the glaucoma patients (-14 dB; Table 1), we get an answer close to -0.2 log unit, i.e., the loss of logCS attributed to glaucoma (Table 2). This tentatively suggests that glaucoma patients with little or no visual field loss would have roughly normal dark and light adaptation plateaus.

Intriguingly, three out of four CS plateaus were significantly lower in women (Table 2), which could not be explained by a gender difference in glaucoma severity or age (P=0.42). Gender differences in CS have been reported before,[30,31] and are consistent with a more pronounced visual illness perception in women than in men with glaucoma.[5] The decrease in CS with increasing age found in our study matches with results observed in clinical and population-based studies.[32–35]

In this study, there was a difference in age distribution between glaucoma patients and controls. We initially included participants between 40 and 75 and aimed for a uniform age distribution. However, since glaucoma is a disease of the elderly, the vast majority of patients with glaucoma within our database was above 60 years of age. This made us recruit additional elderly controls. Nevertheless, a difference in age distribution between the groups remained. The distributions showed considerable overlap and all statistical analyses and graphs were adjusted for age. Therefore, this difference will not have influenced our findings. Albeit not intentionally matched, glaucoma patients and controls did not differ regarding gender (Table 1). Within the glaucoma group, the age distribution did not differ between male and female (P=0.7). This was also the case within the control groups (both P=0.6). As such, there was no collinearity between age and gender in our analysis.

The stimulus used in our experiments was a 1.15 degrees increment presented centrally. Therefore, we assumed to measure primarily cone function. However, the time that was needed to reach the CS plateau after the 6.5 log unit decrease in luminance appeared to be over 20 minutes in the healthy subjects. This suggests some rod involvement as well.[22] A possible explanation for the influence of rods in our experiment could be a less precise fixation during the dark adaptation phase (the fixation target was, despite its high contrast, barely visible especially during the beginning of the dark adaptation phase). In any case, glaucoma patients and healthy controls were susceptible to the same experimental conditions, and the adaptation differences between both groups appeared to be quite consistent. This is the first study that measured light adaptation in glaucoma patients, and focussed on the foveal part of the glaucomatous retina during dark adaptation. Another strength is the unpreceded high luminance of 10,000 cd/m^2 in the second experiment.

No cycloplegia, mydriasis, or artificial pupil was used. An advantage of this approach is that it gives insight in differences in the overall light and dark adaptation performance between glaucoma patients and healthy subjects, as the pupil reflex is one of the mechanisms contributing to adaptation. Another advantage is that it gives a more realistic insight in visual impairment. A clear drawback is that it is more difficult to study the glaucomatous changes in retinal sensitivity. At 320 cd/m^2, the pupil diameter did not differ between the glaucoma patients and the controls (with and without adjustment for age; Table 1). Hence, the observed difference in light adaptation CS

plateau at this luminance cannot be explained by a difference in pupil diameter and could thus be attributed to a difference in retinal sensitivity. We did not measure the pupil diameter at 10,000 cd/m^2. Presumably, a significant part of the observed difference in light adaptation CS plateau at this luminance is caused by a difference in retinal sensitivity as well. At 2 cd/m^2, the pupil was smaller in the glaucoma patients than in the controls (with and without adjustment for age; Table 1), and this may imply a difference in pupil diameter at 0.0032 cd/m^2. Due to the Stiles-Crawford effect, this difference is not relevant to cone adaptation (our primary target), but may play a role in the confounding rod adaptation (see previous paragraph).

The essentially constant offset between the logCS of glaucoma patients and the controls during light and dark adaptation indicates an intact light and dark adaptation mechanism in the strictest sense (rod and cone function) together with an impaired signal processing downstream in the retina and beyond. This is in agreement with the presumed pathophysiology of glaucoma but apparently disagrees with the results of questionnaire studies (see Introduction section), which uncovered clear differences in visual complaints between glaucoma patients and healthy subjects when going from light to dark or dark to light. For dark adaptation, this discrepancy might be explained by postulating that a certain minimum CS is needed for reasonable vision. When adapting to darkness, glaucoma patients need longer to reach this minimum CS, which might explain their complaints when going from light to dark (glaucoma patients and controls had a similar dark adaptation time, but this time was defined as the time needed to reach 50% (-3 dB) of the CS plateau; as glaucoma patients have a lower CS plateau than the controls, they need longer to reach a certain absolute CS value). For light adaptation, the resolution of our sampling (one threshold per 30 seconds) makes it impossible to conclude if something similar plays a role when going from dark to light.

In conclusion, in the apparently intact foveal part of the visual field, glaucoma patients suffer from a reduced contrast sensitivity that is essentially independent of their adaptational state. This indicates an intact function of the outer retina together with an impaired modulation transfer in a later stage. As a result, during dark adaptation glaucoma patients reach a certain CS later than healthy subjects, which might explain their complaints when going from light to dark. Experiments with a better temporal resolution are needed to fully understand the complaints of glaucoma patients when going from dark to light.

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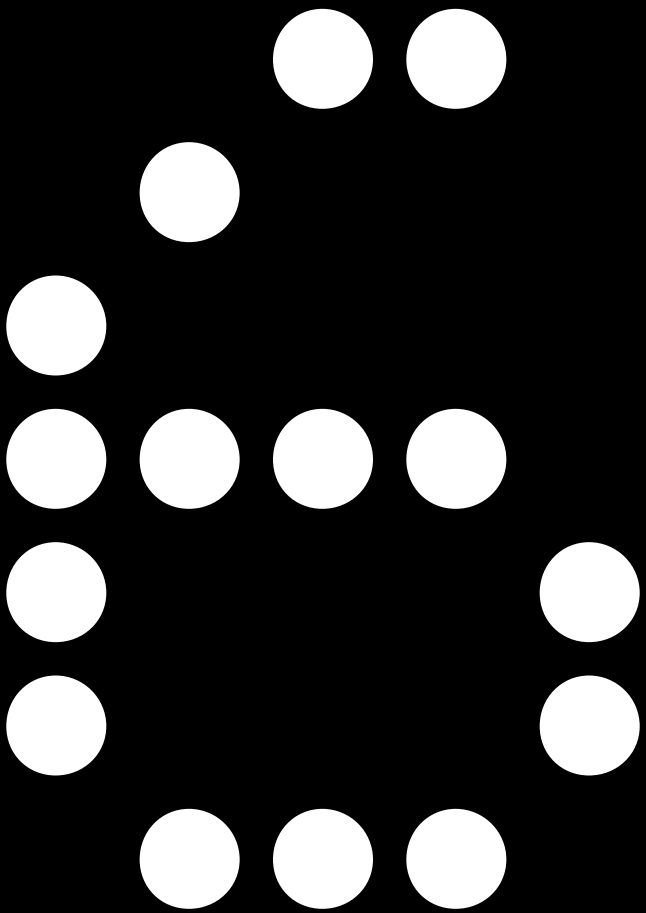

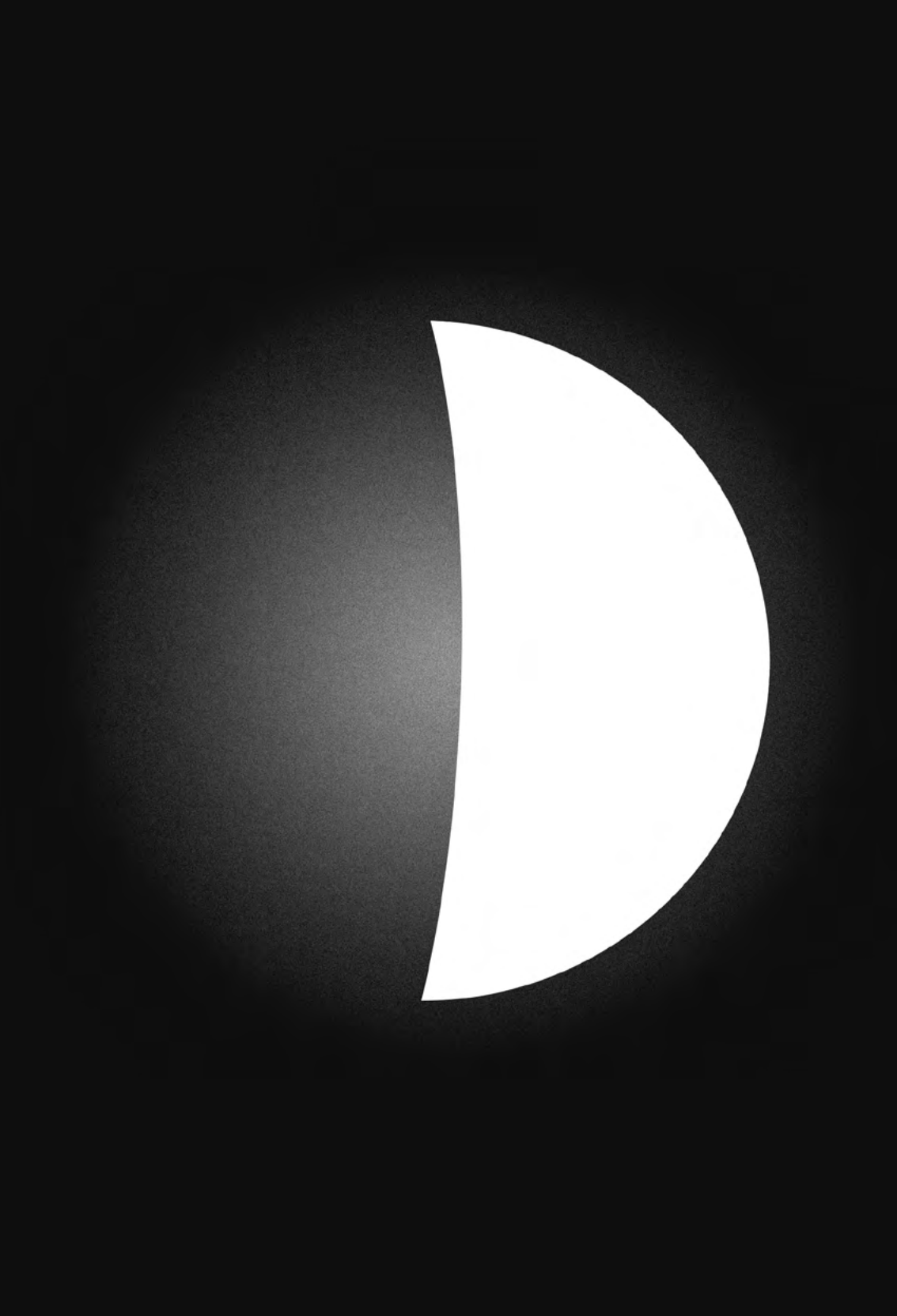

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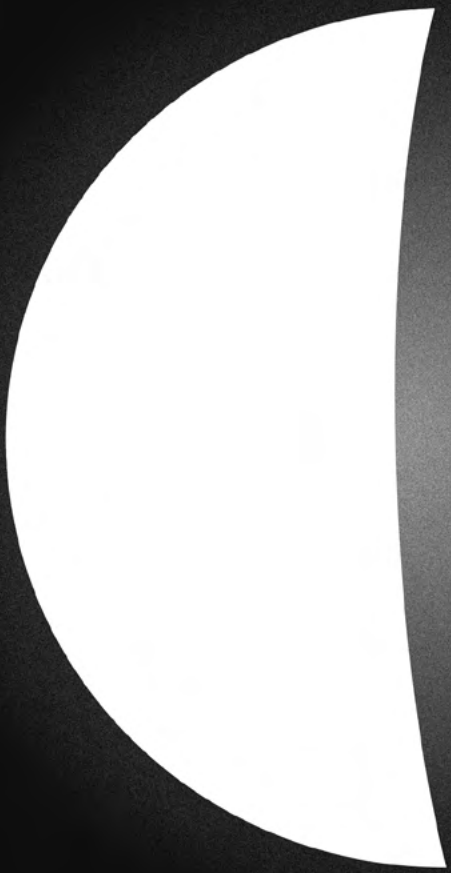

Based on: *Bierings RAJM, Jansonius NM. Luminance and pedestrians' perceived ability to see after dark: mapping the Netherlands using a citizen science network of smartphone users. Light Res Technol. 2018. doi:10.1177/1477153518758355.*

LUMINANCE AND PEDESTRIANS' PERCEIVED ABILITY TO SEE AFTER DARK: MAPPING THE NETHERLANDS USING A CITIZEN SCIENCE NETWORK OF SMARTPHONE USERS

ABSTRACT

Purpose: To determine (1) pedestrians' perception of their ability to see when walking in an outdoor public space after dark, specifically those instances considered to offer insufficient ability to see (visual complaint), (2) the luminance distribution of the pavement after dark, and (3) the association between these complaints and luminance.

Methods: We recruited a citizen science network of smartphone users who, by using an app, reported the amount of visual difficulty outside after dark in their own neighbourhood and measured the corresponding amount of light. Participants were stratified according to the self-reported presence or absence of an eye disease. Logistic regression was used to determine the influence of luminance, age, gender, and eye disease on reported ability to see after dark.

Results: Amongst those respondents who did not report an eye disease, 11% reported visual conditions they perceived to make walking difficult; this increased to 40% for pedestrians who reported an eye disease. The recorded luminances were typically 0.01–0.1 cd/m^2. Visual complaints of pedestrians to walk outside after dark were more pronounced in women (P=0.033) and participants with an eye disease (P<0.001), and below a luminance of 0.01 cd/m^2 (P=0.010).

Conclusions: One in ten ophthalmic healthy persons has visual complaints regarding walking outside in the public space after dark, compared to two in five persons with an eye disease. Especially the visually disabled experience an increase in visual difficulties with decreasing luminance, which probably has an impact on their mobility after dark.

INTRODUCTION

Visual performance worsens with decreasing luminance,[1–4] and as luminance decreases, the likelihood of road accidents increases.[5] Therefore, public lighting is intended to enhance visibility and safety for road users in outdoor public spaces after dark.[6] Although motorized traffic and slow-moving traffic like pedestrians may have different visual needs, the luminance of the road is of great importance for both groups.[7–10]

The eyes of a motorist are mainly focused on the road ahead and assisted by headlights.[9,11,12] Pedestrians, on the other hand, have to detect obstacles without headlights (physical security), should be able to identify the intentions of others (social security), and should achieve a sufficient amount of visual orientation.[6,13–15] Since different surfaces with different reflectances are involved in these visual tasks, the illuminance rather than the luminance is the basic lighting parameter that is used for pedestrian lighting recommendations.[9,10] A minimal illuminance for pedestrian areas has been recommended.[6,14] However, it is luminance rather than illuminance that determines visual performance (the effect of snow and recent industrial efforts to develop high-reflectance asphalt point to this). In the eye-tracking study of Fotios et al., pedestrians' viewing behaviour in the public space after dark was explored using a dual task approach.[16] Although dependent on the characteristics of the path and the presence of other pedestrians, the path resulted in the highest proportion of observations, and the near path (within 4 meter) was found to be more important than the far path. This makes knowledge regarding the luminance distribution of the pavement in the public space after dark pivotal, but this knowledge seems scarce, as seems to be the case for knowledge regarding the minimum luminance that is considered sufficient to walk (see Discussion section). Furthermore, the minimum luminance needed to walk might differ between people with healthy eyes and people with an eye disease.[17–21]

The aim of this study was to determine (1) pedestrians' perception of their ability to see when walking in an outdoor public space after dark, specifically those instances considered to offer insufficient ability to see (visual complaint), (2) the luminance distribution of the pavement after dark and (3) the association between these complaints and luminance. For this purpose, we recruited a citizen science network of smartphone users who, by using an app, reported the amount of visual difficulty outside after dark in their own neighbourhood and measured the corresponding amount of light. Participants were stratified according to the self-reported presence or absence of an eye disease.

METHODS

Study population

The start of this project was part of the National Science Weekend 2015 in the Netherlands – a national event showcasing science to the general public. This weekend was organized in the International Year of Light (2015). Participants were recruited through national and regional advertising. They were asked to download the app 'Zicht op Licht' (translated: Insight into Light) to their smartphone and to conduct measurements in their own street after dark. In addition, all the third-year high school children (aged 13 to 15 years) of one high school in Leek (a town with approximately 20,000 residents, situated in the north of the Netherlands), participated in the context of their research project. Their task was to systematically map all streets of the town of Leek, in order to assess a potential selection bias regarding the distribution of luminances throughout the Netherlands.

The study protocol was approved by the ethics board of the University Medical Center Groningen (UMCG). The download and use of the app were voluntary and the app could be deleted at any time. The study followed the tenets of the Declaration of Helsinki.

Data collection

An iOS app was built to measure low luminances on the surface one metre in front of the feet of the participant, through the camera of an iPhone. Technically, the app was based on the Dark Sky Meter app (www.darkskymeter.com); the Dark Sky Meter app was modified for our study by its maintainer. The app was calibrated with a Minolta luminance meter with built-in photometric filter (LS-110; Minolta Camera Co. Ltd., Japan). The lowest value displayed by the Minolta was 0.01 cd/m^2. However, the output of the app still decreased monotonically with decreasing luminances below 0.01 cd/m^2. On the other side, the app saturated at 1 cd/m^2. For this reason, recorded luminances were categorized as either <0.01, 0.01 to 1 or >1.0 cd/m^2. Valid measurements could be performed with iPhone models 4S, 5, 5C, 5S and 6.

When the app was opened for the first time, participants filled in their personal information: age, gender, the presence of an eye disease, and email address. If participants reported an eye disease, they could specify whether this was glaucoma, macular degeneration, cataract, diabetic eye disease, or other/more than one/unknown. Subsequently, they were asked to go to an outdoor place, anywhere, outside after dark, to perform a luminance measurement. At the start of each new measurement, participants filled in some multiple choice questions regarding the environment: if they were inside or outside; if they stood somewhere in the public space or in their own garden or yard; if there were street lights; and if they were in a village, town, city, or in a rural area.

The luminance measurement was initiated by a button on the screen. Before doing this, participants were instructed (by both text and an illustration) to aim the camera of their smartphone 1 m in front of their feet. During development of the app, we found, by making pictures with the smartphone in different positions, that 1 m was

the best distance for actually assessing only the pavement, rather than including either the participant's shoes or any object or light at distance. Measurements with the Minolta luminance meter showed that there was no systematic effect of distance between 1 and 4 meter (the region within 4 meter was found to be most important for pedestrians).[16,22] The luminance measurement itself took approximately 10 seconds.

Immediately after the measurement, the following question was displayed on the screen: 'Hoeveel moeite heeft u hier met het zien om u voort te kunnen bewegen?' (in English: 'How much difficulty do you have with seeing to walk at this place?'). We hereafter use the term visual complaint to describe this question. The response options are described below. After all of the questions were answered, the measurement ended with some feedback to the participant regarding the measured amount of luminance and the sending of the data via internet to our database. With GPS coordinates, every measurement also appeared on an online available map. Altogether, a measurement took less than one minute.

An Android app was built that was identical to the iOS app, but without the actual luminance measurement – it was not possible to include the luminance measurement in the Android app because of the many different brands and types of Android smartphones. In total 70 individuals, half of whom were iPhone users, contributed to the development of the app by testing and providing feedback in the various stages of the development. At the time of submission of this paper, neither the iOS nor Android apps were available due to maintenance costs (every update of the operating system implied thorough testing and calibrating of the app for each iPhone type; we ceased doing this after the data collection; reactivation is possible as the app is a modification of a currently maintained app [see above]).

The data collection started on the first of October 2015 and ended the first of February 2017. Once a month, participants were reminded by an email and a push message to perform a measurement.

Data analysis

All measurements that were performed inside, or outside during daylight, were excluded from further analysis. Individual iPhone participants were identified by a unique device ID; Android smartphone users by their email address (due to there being many different types of Android smartphone, it was not possible to unambiguously label a unique Android device). If the email address of a measurement with an Android device was missing, we excluded the measurement from further analysis. Measurements that were performed with unsupported iPhones were analyzed as measurements with an Android device (i.e., without the luminance measurement). The study population was described using nonparametric descriptive statistics (median with interquartile range [IQR]). Univariable comparisons of continuous variables between participants with and without an eye disease were made with a Mann-Whitney test; proportions were compared by a Chi-square test with Yates' correction.

To determine the prevalence of visual complaints in outdoor public spaces, we excluded all measurements that were performed in a garden or yard. Subsequently, we

selected only one measurement per unique participant. Some participants measured more than once at a single location, or at multiple locations, or both. If a participant measured more than once, we included only one measurement per participant, being (arbitrarily) the second measurement, independent of the location. Questions regarding visual complaints contained four response options. We dichotomized these response options into two categories: No complaints and Complaints in order to be able to calculate a prevalence and to perform logistic regression. The response options 'No difficulty at all' and 'A little difficulty' were categorised as *No complaints*; the response options 'A lot of difficulty' and 'Extreme difficulty' were categorised as *Complaints*. We performed logistic regression to determine the influence of age, gender, and eye disease on the presence of visual complaints after dark.

To determine the luminance distribution of the outdoor public spaces after dark, we selected all iPhone measurements. Again, all measurements that were performed in a garden or yard were excluded. We used a histogram and nonparametric descriptive statistics (median with [IQR]) to describe the distribution of pavement luminance after dark within the Netherlands. Measurements in Leek were selected with GPS coordinates (latitude between 53.138 and 53.184 degrees; longitude between 6.350 and 6.395 degrees) and presented separately. The luminance distributions for measurements (A) throughout the Netherlands except the town of Leek and (B) Leek were compared using a Chi-square test after stratification in four categories (<0.01, 0.01–0.1, 0.1–1 and >1 cd/m^2).

To determine the association between luminance and complaints, we selected only one measurement per iPhone user. If a participant measured more than once, the second measurement was selected (see above). Based on the luminance frequency distribution, the measurements were divided into three groups: a low luminance group, an intermediate luminance group, and a high luminance group (see Results section). We used a bar chart to describe the prevalence of visual complaints per luminance group, for participants with and without eye disease. The influence of luminance, age, gender, and eye disease on the presence of visual complaints after dark was determined using logistic regression.

All analyses were performed using R (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria). A P value of 0.05 or less was considered statistically significant.

RESULTS

Figure 1A shows a map of the Netherlands with the 6709 measurements performed by 1857 individual participants. Figure 1B, an enlargement of the north-eastern region of the Netherlands, shows a map of Leek with the subset of 2683 measurements performed by 110 individual participants. After the exclusion of inappropriate measurements (those that were done inside, not in a public space, during the day, or for which a unique participant could not be identified), 3813 measurements belonging to 780 unique participants (of which 54 were from Leek) were available for further analysis.

Table 1A shows the characteristics of the unique participants without (n=717) and with (n=63) a self-reported eye disease, who performed one or more measurements. The prevalence of visual complaints outside after dark was 10.9% (78 of 717) for participants without an eye disease (men: 7.1%, women: 14.9%) and 39.7% (25 of 63) for participants with an eye disease (men: 32.1%, women: 45.7%). Table 2A shows the corresponding logistic regression analysis. Women and especially participants with an eye disease reported more visual complaints (odds ratio [OR] for eye disease 4.88, that is, after adjustment for age and gender, participants with an eye disease are approximately 5 times more likely to have visual complaints after dark compared to those without an eye disease).

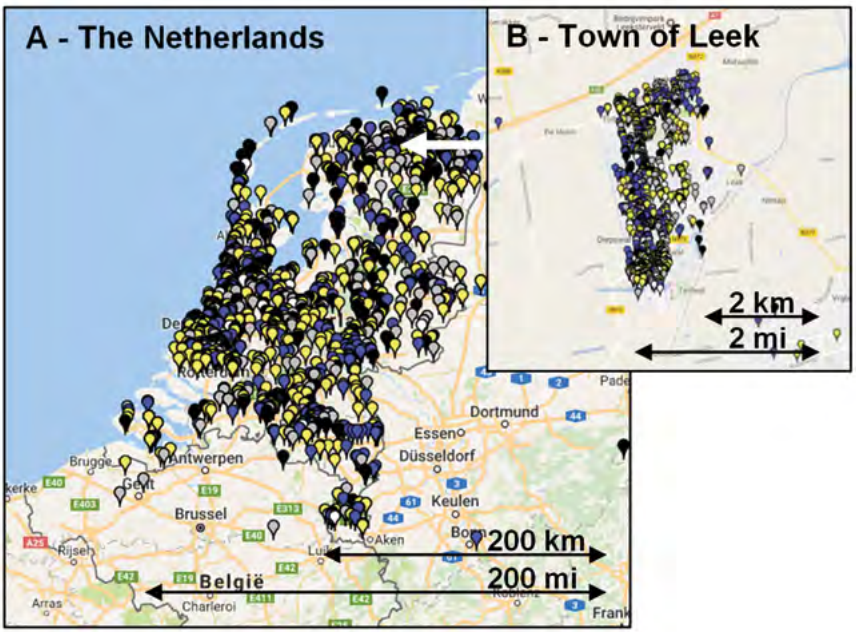

Figure 1. *Distribution of measurements throughout the Netherlands (A) and the town of Leek (B).*

Table 1. *Characteristics of the entire study population (A) and the subset of iPhone users (B).*

	Table 1A		
	Participants without eye disease (n=717)	Participants with eye disease (n=63)	P value
Age (year; median [IQR])	45 (30 to 57)	56 (43 to 67)	<0.001
Gender (% female)	43	56	0.066
Eye disease	NA	Glaucoma: n=26 Macular degeneration: n=6 Cataract: n=2 Other: n=29	NA
	Table 1B		
	Participants without eye disease (n=339)	Participants with eye disease (n=34)	P value
Age (year; median [IQR])	47 (34 to 57)	53 (43 to 67)	0.002
Gender (% female)	38	41	0.87
Eye disease	NA	Glaucoma: n=8 Macular degeneration: n=3 Cataract: n=2 Other: n=21	NA

IQR = interquartile range; NA = not applicable; Other = other/more than one/unknown.

Table 2. *Odds ratios of visual complaints of pedestrians to walk outside in the public space after dark for the entire study population (A) and the subset of iPhone users (with luminance measurement; B).*

	Table 2A	
	OR (95% CI)	P value
Age (per year)	1.00 (0.99 - 1.02)	0.57
Gender (female)	2.21 (1.39 - 3.52)	<0.001
Eye disease	4.88 (2.68 - 8.88)	<0.001
	Table 2B	
	OR (95% CI)	P value
Age (per year)	1.02 (0.99 - 1.04)	0.15
Gender (female)	2.13 (1.06 - 4.28)	0.033
High luminance	*Reference*	-
Intermediate	1.71 (0.39 - 7.45)	0.48
Low luminance	5.27 (1.48 - 18.8)	0.01
Eye disease	4.92 (2.01 - 12)	<0.001

OR = odds ratio; CI = confidence interval.

Of the abovementioned 3813 measurements in outdoor public spaces after dark, 2431 (of which 1585 from Leek) were performed with an iPhone, and thus included a luminance measurement. These iPhone measurements were performed by 232 unique participants (32 from Leek), with a median (IQR) number of measurements per participant of 1 (1 to 4) outside Leek and 34 (18 to 55) within Leek. Figure 2A shows the luminance distribution outside in the public space after dark for the Netherlands except Leek; Figure 2B shows these data for Leek. The vast majority of the measurements (93%) were conducted in an environment with street lights. The median (IQR) luminance was 0.019 cd/m^2 (<0.010 to 0.050) and 0.057 cd/m^2 (0.021 to 0.134), for the Netherlands and Leek, respectively. These distributions differed significantly (P<0.001).

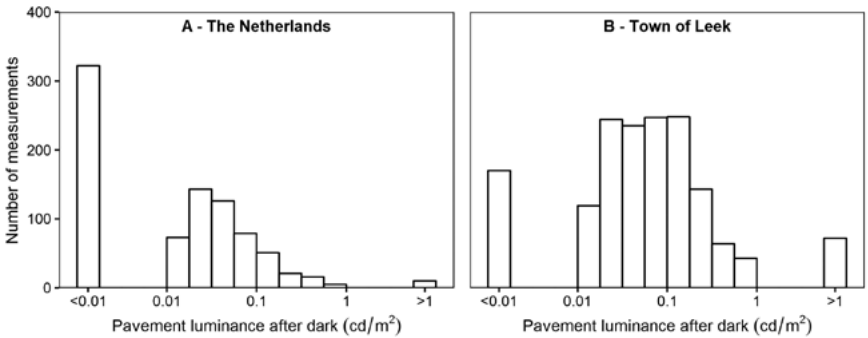

Figure 2. Frequency distribution of pavement luminance at night for measurements throughout the Netherlands except the town of Leek (A) and Leek (B).

In total, 2848 iPhone measurements were performed outside after dark, the abovementioned 2431 in public spaces and another 417 in the garden or yard. These 2848 measurements belonged to 373 unique participants, of which 34 self-reported an eye disease. Table 1B shows the characteristics of these 373 unique participants with and without eye disease. More than half of the measurements (n=200) yielded a luminance of less than 0.01 cd/m^2 and therefore a luminance below 0.01 cd/m^2 was defined as the low-luminance category. We then took the median of the remaining measurements (n=173) to define the cut-off luminance between the intermediate-luminance and high-luminance category. This cut-off luminance was 0.04 cd/m^2. Figure 3 presents the percentage of participants with and without an eye disease with visual complaints, for the three different luminance categories. The percentage of participants with complaints differed between those with and without an eye disease for the low (P=0.001) and intermediate (P=0.01) luminance category, but not for the high luminance category (P=0.89). For those without an eye disease, the percentage of participants with complaints increased especially below 0.01 cd/m^2; for those with an eye disease, the increase started at higher luminances. Table 2B shows the corresponding logistic regression analysis. Women and participants with an eye disease reported more complaints, and these complaints were more pronounced in the low-luminance category.

DISCUSSION

The prevalence of visual complaints of pedestrians without an eye disease to walk outside after dark is 11%. The luminance of the pavement in the public space after dark is typically in the range of 0.01-0.1 cd/m^2. Visual complaints of pedestrians to walk outside after dark are more pronounced in women and participants with an eye disease, and below a luminance of 0.01 cd/m^2.

Eye-tracking experiments revealed that, after dark, pedestrians spend a significant amount of their time observing the pavement, with a tendency to concentrate at the near (that is, within 4 m) path.[16,22] Intriguingly, we could not find any study that linked the luminance of the pavement directly to visual complaints regarding walking outside after dark. Several questionnaire studies asked for visual performance outside after dark.[21,23–25] The questions, however, either addressed other tasks (e.g. driving) or did not address a specific task. For example, the question 'Do you have difficulty seeing at night'[25] may relate to mobility, but also to facial expression discrimination, spatial orientation, or glare disability, and all these factors contribute to visual comfort.[9,13,15,26–35] In a recent questionnaire study, we tried to avoid this ambiguity by specifying the task explicitly. Our question 'Because of your eyesight, how much difficulty do you have with walking or cycling at night on an unlit country road' yielded a prevalence of visual complaints of 14% in subjects without an eye disease and 54% in patients with glaucoma.[36] These percentages are in good agreement with that of the low luminance category shown in Figure 3.

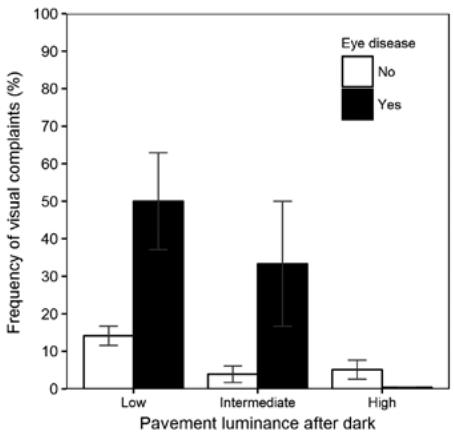

Figure 3. Frequency of visual complaints as a function of the pavement luminance after dark for participants with and without an eye disease. Low luminance was below 0.01 cd/m^2, intermediate luminance between 0.01 and 0.04 cd/m^2, and high luminance above 0.04 cd/m^2. Error bars denote +/- 1 standard error.

Two studies related a subjective rating of visual comfort with the amount of light in the public space after dark.[37,38] Both studies used a 9 point appraisal scale and determined the luminance that was appraised as poor to adequate (Simons et al.)[37] and inadequate to fair (De Boer)[38]; in both studies this corresponded to point 4 on the 9 point scale. Simons et al. reported a threshold of 2.5 lux (0.08 cd/m^2 assuming a reflectance of 0.1 [see

below]);[37] De Boer reported a threshold of 0.2 cd/m^2 to reach a visual comfort deemed acceptable.[38] These studies were based on 25 and 16 observers, respectively, and did not specify a task but rather asked for a general appraisal.[37,38] In addition, in both studies the observers visited all sites. Therefore, it is possible that the range of luminances that was presented influenced the rating itself (range bias), resulting in biased thresholds. These differences might explain why their thresholds seem somewhat high compared to our findings (Fig. 3). Several studies have addressed the influence of light on performance in a laboratory setting. Boyce et al.,[39] Simmons et al.,[40] and Jaschinski et al.[41] measured speed in an emergency setting and recommended illuminances of 0.3 to 2 lux. Assuming the floor to be a Lambertian surface (perfectly diffuse reflecting surface with reflectance 1), this would correspond to a luminance of 0.1 to 0.6 cd/m^2. The floor, however, absorbs part of the light. The reflectance of the street or pavement has been reported to be typically 0.07.[42] We measured the reflectance of the default Dutch paving stone to be 0.15 and that of asphalt 0.12. Assuming a reflectance of 0.1, 0.3 to 2 lux would yield 0.01 to 0.06 cd/m^2. This suggests that the pavement luminance after dark is just about enough to reach the abovementioned recommendations.

Studies investigating obstacle detection, found that the largest increase in detection rate occurred between 0.2 and 2 lux.[8,42,43] Depending on the reflectance of the obstacles, this corresponds roughly to 0.01 to 0.1 cd/m^2, which is in agreement with the decrease in complaints from the low to the moderate category shown in Figure 3. International and national quality criteria for public lighting for roads that are used by motorized traffic, state a minimum average luminance after dark of 0.3 cd/m^2. For roads that are used by pedestrians or slow traffic, there is no minimum luminance criterion but a minimum illuminance criterion, being 0.4 lux.[6,14] With a paving stone reflectance of 0.1, this corresponds to 0.013 cd/m^2. Figure 3 shows that the threshold for visual complaints for participants without an eye disease is lower than 0.01 cd/m^2, whereas for participants with an eye disease it is higher than 0.04 cd/m^2. Therefore, the minimum criterion of 0.013 cd/m^2 seems to be sufficient for people with healthy eyes but not for those with an eye disease.

The influence of gender on visual complaints (Table 2) is consistent with earlier studies that used either subjective and objective outcome measures.[20,36,44,45] Although we specifically asked for difficulties with seeing to walk, our results could also be explained by a general feeling of insecurity after dark in women.[46,47] Although the effect of age on visual performance as, for example, contrast sensitivity is undeniable,[48–51] we did not find an influence of age on visual complaints. A possible explanation of this apparent discrepancy is the fact that the effect of age on contrast sensitivity – albeit highly significant – is small compared to the effect of luminance. For example, Nio et al.[51] found a decrease in contrast sensitivity of typically 0.3 log units between 20 and 70 years of age; a decrease in luminance from 0.1 to 0.01 cd/m^2 already results in a 0.5 log units decrease in contrast sensitivity.[52,53] Nio et al. performed their measurements at a mean luminance of 200 cd/m^2. Age could be a more important factor in case of a low luminance. We repeated the analysis presented in Table 2B for the lowest luminance category subset; the OR for age increased slightly (OR 1.03 (1.00-1.07); P=0.06).

To ensure that the participants could perform the measurement, the instructions were displayed both in text and graphically, and the app was adjusted until it was

understandable for subjects of all ages. We used two control questions to exclude measurements that were performed inside and not in the public space, and we excluded measurements that were performed with daylight. However, it could be the case that participants who live in a low- or high-luminance environment were more motivated to contribute. To assess this potential bias, we used the school project to map one town (Leek) in detail. When comparing the luminance distribution of the measurements throughout the Netherlands except Leek (Fig. 2A), with that of Leek (Fig. 2B), the overall picture agrees well but there seems to be a small bias towards low luminances. Another explanation of this difference could be a real luminance difference between Leek and other towns, villages, and cities in the Netherlands. Of all luminance measurements performed outside after dark, 23% were reported to be performed outside a village, town, or city, that is, in a rural area (27% in Leek and 17% throughout the Netherlands). Bias could also arise from the fact that participants reported difficulties just because they assumed darkness implies difficulties. The effect of this bias seems limited; we found a clear dose-response relationship and a clear effect of eye disease, and a low percentage (only 5%) of difficulties in those without an eye disease being in an above average luminance situation (Fig. 3).

Our citizen science project was inspired by an earlier project in the Netherlands, where atmospheric aerosols where mapped using a citizen science network of smartphone users.[54] A difference with that and other projects, is that we did not only collect data from the environment but also from the citizen scientists themselves. An advantage of using a citizen science network in general is the arousal of public awareness, in this study specifically regarding the influence of luminance on the accessibility of the public space after dark. It is possible to perform a large number of luminance measurements with only a few observers (as we did in Leek), and these measurements could be even more accurate. However, a realistic inventory of complaints requires a large number of unique subjects that can be considered a representative sample of the general population – for which the citizen science approach is pivotal. The technology that is offered by tablets and smartphones might enable screening or follow-up of diseases in the foreseeable future. This could be helpful to unburden the healthcare system; due to the fast increase in the number of elderly in the upcoming decades, self-reliance by technology might be necessary. Despite the high potential, medical citizen science projects are still rare compared to other disciplines.[55] A disadvantage of the citizen science approach is the potential for suboptimal data quality and a selection bias, which we addressed in the previous paragraph.

The luminance of the pavement might be more critical for the visually disabled than it is for those with healthy eyes.[7] Although the group size was small, when going towards lower luminances, visual complaints of participants with an eye disease increased earlier compared to participants without an eye disease (Fig. 3). This corroborates with earlier questionnaire studies, which found a higher frequency of visual complaints after dark in subjects with an eye disease.[19,21,25] Kuyk et al. studied the duration of an outdoor walk, and the number of mobility incidents, in older adults with low vision with a high (>1000 cd/m^2) and a moderate (7 cd/m^2) surface luminance.[7] Although their lower luminance was typically 2 log units higher than the luminances we found outside in the public space after dark, they already found a significant increase in the duration and number of mobility incidents with the lower luminance, illustrating the

disproportional disability of people with an eye disease after dark.[7] It seems obvious that this could have an effect on the mobility after dark and thereby the quality of life of the visually disabled.[56]

In conclusion, one in ten ophthalmic healthy persons has visual complaints regarding walking outside in the public space after dark, compared to two in five persons with an eye disease. Especially the visually disabled experience an increase in visual difficulties with decreasing luminance, which probably has an impact on their mobility after dark. The citizen science approach allowed us to make an estimate of the luminance of the public space and its influence on visual complaints. Future studies could focus on the actual measurement of mobility after dark, and might work towards a minimum luminance criterion for the pavement.

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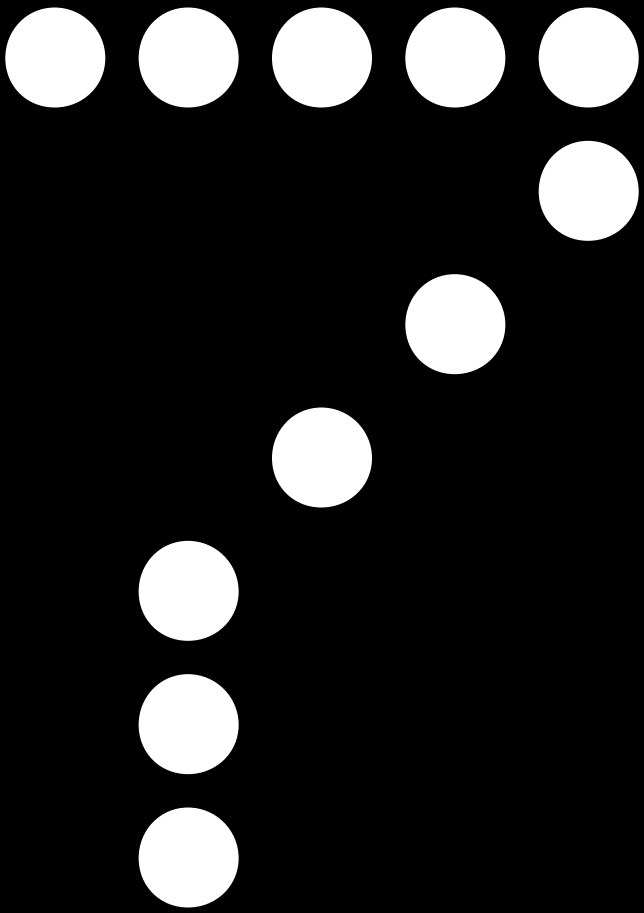

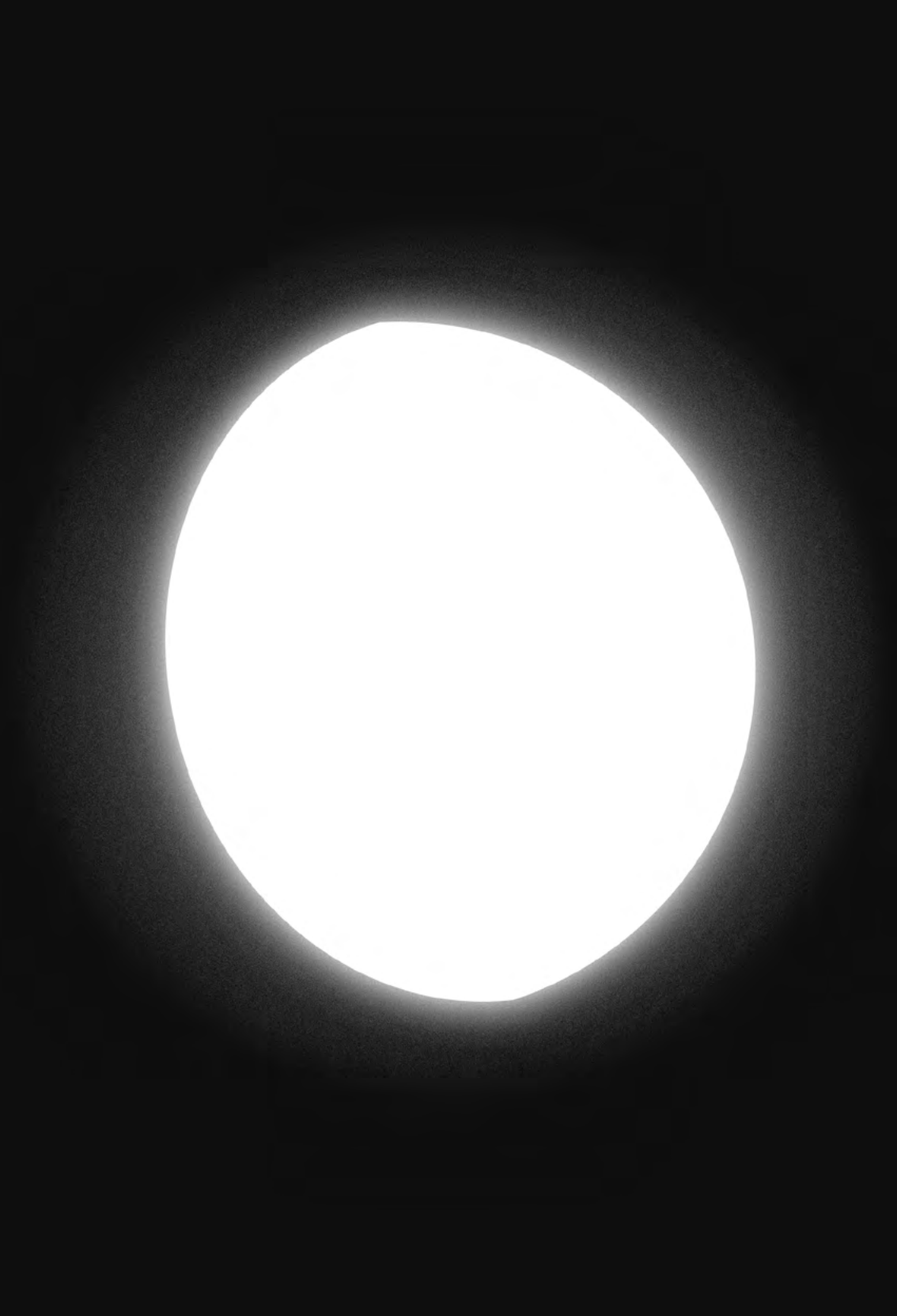

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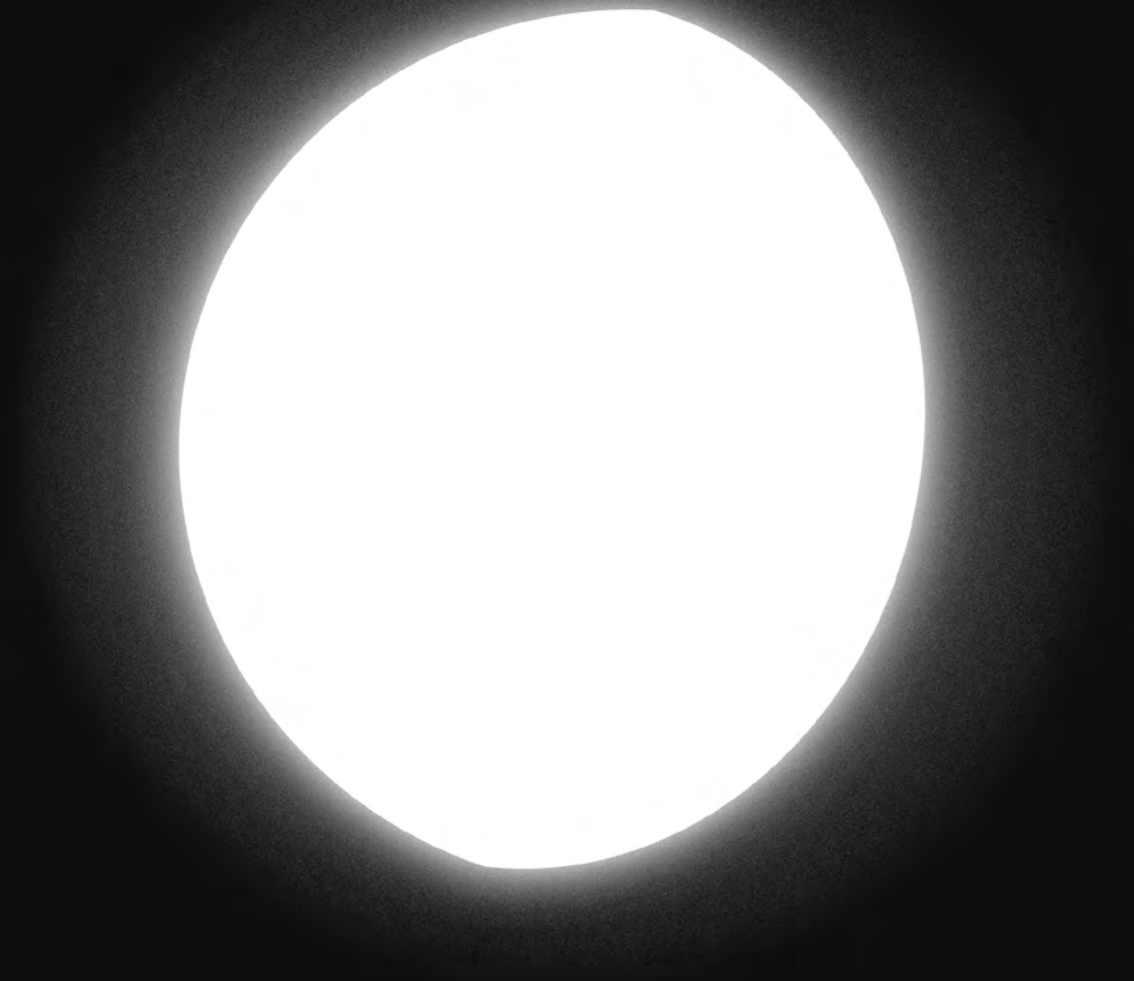

Submitted

CHRONOTYPING GLAUCOMA PATIENTS WITH THE MUNICH CHRONOTYPE QUESTIONNAIRE: A CASE-CONTROL STUDY

ABSTRACT

Purpose: The circadian clock is entrained to light by the intrinsically photosensitive retinal ganglion cells. Loss of these cells in glaucoma, an eye disease with loss of retinal ganglion cells as its key feature, might thus result in a change in chronotype. We aimed to compare chronotype distribution between glaucoma patients and healthy subjects.

Methods: We sent the Munich ChronoType Questionnaire to 221 glaucoma patients (response rate 81%); controls (182) were primarily their spouses. After exclusion of shift workers and participants who woke-up due to an alarm clock on days off, 159 glaucoma patients (88 early, 21 moderate, and 23 severe glaucoma) and 163 controls remained. We calculated chronotype as the mid-sleep on days off, corrected for workweek accumulated sleep debt (MSF_{sc}). We compared means and variances between groups using Welch's tests and F-tests, respectively.

Results: Glaucoma did not affect the mean MSF_{sc} (controls 3:47h; early, moderate, and severe glaucoma 3:40h, 3:45h, and 3:33h, respectively [P=0.62]). Chronotype variability increased with increasing disease severity (severe glaucoma versus controls: P=0.023).

Conclusions: The entrained phase of the sleep-wake cycle in patients with early or moderate glaucoma is not significantly different from the entrained phase in healthy subjects. With increasing glaucoma severity, chronotype variability seems to increase without a clear shift of the distribution. This indicates that some patients may advance and others delay their sleep phase with increasing symptom severity. Future studies might focus on a more in-depth analysis of the role of the circadian clock in severe glaucoma and related disturbance of their quality of life.

INTRODUCTION

Glaucoma is a chronic and progressive eye disease characterized by loss of retinal ganglion cells (RGCs) and subsequent visual field loss. Among the different types of RGCs, the intrinsically photosensitive retinal ganglion cells (ipRGCs) express melanopsin and are held responsible for nonvisual responses to light, such as the pupillary light reflex[1–3] and the entrainment of the circadian clock to light.[4–8] Output of the ipRGCs is transmitted to the suprachiasmatic nucleus, the circadian clock that drives rhythms with a period of approximately 24 hours in physiology, sleep-wake behaviour, and cognitive performance.[9–11] In absence of light cues, the circadian system will lose its synchronisation to the Earth's 24-hour light/dark cycle, the Zeitgeber,[12,13] and this leads to a mismatch between endogenous rhythms and the sleep-wake cycle. Hence, loss of ipRGC function in glaucoma might result in circadian misalignment and thus disturb the sleep quality and pattern of glaucoma patients.[14] Interestingly, the light-induced melatonin suppression, as one of the nonvisual responses to light, was found to be affected in patients with advanced glaucoma,[15–17] and glaucoma patients often do report a lower sleep quality.[18–21] It is controversial, however, if the latter is related to RGC damage or to psychological factors.[22]

Human circadian phase can be described by means of the chronotype of an individual. The chronotype of an individual can be defined as the midpoint between sleep onset and wake-up time on days off[23] corrected for sleep on working days.[24] The chronotype as defined by sleep phase should be considered as a marker of circadian phase, and it has been shown to correlate well with other circadian phase parameters such as the start of melatonin production.[24–27] Functional damage of ipRGCs might lead to misalignment of the circadian clock to light resulting in either freerunning patterns of sleep and wakefulness, or to modulations of the direct effects of light on sleep and wakefulness.[4,28] The intrinsic period of the circadian clock in humans differs between individuals and is on average a little bit longer than 24 hours.[13,29–31] The entrained phase of the circadian pacemaker is dependent on the intrinsic period showing a later sleep phase with longer intrinsic period.[25,32–34] Consequently, damage to the ipRGCs in glaucoma might result in a delay of the mean MSF_{sc} and an increase in sleep phase variability. A delay and an increase in variability in activity onsets has indeed been found in animal studies to glaucoma.[35,36] More variability in waking time was also observed in a diverse group of young subjects with an optic nerve disease, including some patients with glaucoma.[37] Intriguingly, studies to the entrained circadian phase of glaucoma patients appear to be completely lacking.

The aim of this study was to compare chronotype as a measure of circadian phase between glaucoma patients and healthy subjects. For this purpose, we performed a questionnaire study with the Munich ChronoType Questionnaire (MCTQ) and determined the chronotype distribution amongst a large group of glaucoma patients and controls.

METHODS

Study population and data acquisition

The MCTQ was sent by mail to 221 glaucoma patients (cases) with primary open-angle glaucoma, pseudoexfoliation glaucoma, or pigment dispersion glaucoma, selected from the database of the Groningen Longitudinal Glaucoma Study.[38] The disease severity was determined by the mean deviation (MD) value of the better eye (eye with the higher MD value). Controls were primarily the spouses of the glaucoma patients. The ethics board of the University Medical Center Groningen (UMCG) approved the study protocol (METc 2014.338). All participants provided written informed consent. The study followed the tenets of the Declaration of Helsinki.

Table 1. *Characteristics of the study population.*

	Glaucoma patients (n=159)	Controls (n=163)	P value	Missing (%)
Age (year; mean [SD])	72.2 (10.0)	65.9 (10.5)	<0.001	0.0
Gender, female, n (%)	77 (48%)	105 (64%)	0.005	0.0
BMI (kg/m^2; mean [SD])	26.2 (4.7)	26.1 (4.9)	0.81	5.3
Smoker, n (%)	15 (9.4%)	16 (9.8%)	1.0	0.0
Working days per week (days; median [IQR])	0 (0 to 0)	0 (0 to 3)	0.004	5.3
HFA MD of the better eye (dB; median [IQR])	-4.5 (-10.7 to -1.9)	NA	NA	0.0

SD = standard deviation; BMI = body mass index; IQR = interquartile range; HFA MD = mean deviation of Humphrey Field Analyzer; NA = not applicable.

Data analysis

Shift workers and participants who woke-up due to an alarm clock on days off were excluded from the analyses. The study population was described using descriptive statistics. Univariable comparisons between cases and controls were made with a t-test or Mann-Whitney test, depending on the distribution, for continuous variables; for proportions we used a Chi-square test with Yates correction.

For questions regarding bedtime information on days off, the mean and standard deviation (SD) were determined for glaucoma patients and controls. Sleep onset was calculated as the sum of the point of time to get ready to fall asleep, and the length of time needed to actually fall asleep (Q2 and Q3 from Table 2). The sleep duration was defined as the difference between the calculated sleep onset and the wake-up time (Q4 from Table 2). The mid-sleep on days off (MSF) was defined as the midpoint between sleep onset and wake-up time. When the sleep duration during the workweek was shorter compared to that of days off, we corrected the MSF (MSF_{sc}) for workweek accumulated sleep debt.[24] We compared means with a Welch's t-test (unlike the default t-test, this test allows for unequal variances) and distributions with an F-test. For the MSF_{sc}, we also performed a comparison after stratification to disease severity (early glaucoma: MD of better eye above -6 dB; moderate glaucoma: MD between -6 and -12 dB; severe glaucoma: MD below -12 dB) using a Welch F-test (an alternative

to one-way analysis of variance (ANOVA) that does not assume the variances to be equal) to compare means and F-tests to compare variances. A P value of 0.05 or less was considered statistically significant.

Table 2. MCTQ derived bedtime information on days off.

	Glaucoma patients (n=159) Mean (SD)	Controls (n=163) Mean (SD)	P value for Mean (SD)	Missing (%)
A. Questionnaire results				
Q1. I go to bed at ... o'clock	23:24 (0:55)	23:27 (0:46)	0.56 (0.013)	5.6
Q2. I actually get ready to fall asleep at ... o'clock	23:42 (0:53)	23:48 (0:45)	0.36 (0.025)	7.5
Q3. I need ... minutes to fall asleep	0:16 (0:15)	0:16 (0:17)	0.71 (0.036)	9.6
Q4. I wake up at ... o'clock	7:25 (1:11)	7:37 (1:07)	0.13 (0.23)	7.1
Q5. After ... minutes I get up	0:29 (0:39)	0:25 (0:27)	0.24 (<0.001)	6.8
Q6. After ... minutes I feel awake	0:07 (0:13)	0:07 (0:14)	0.81 (0.29)	7.5
Q7. The quality of my nightrest (1-10)	6.7 (1.7)	6.9 (1.6)	0.37 (0.29)	4.3
Q8. Hours spent outside	2:50 (2:02)	2:48 (1:41)	0.84 (0.013)	6.8
B. Calculated variables				
Sleep onset	23:58 (0:56)	00:04 (0:49)	0.32 (0.046)	11.2
Sleep duration	7:28 (1:12)	7:33 (1:08)	0.58 (0.28)	12.1
MSF_{sc}	3:40 (0:53)	3:47 (0:48)	0.21* (0.15)	13.7

* = age- and gender-adjusted P value 0.91.

RESULTS

We retrieved 178 questionnaires from 221 glaucoma patients (response rate 81%) and 182 questionnaires from controls. After exclusion of shift workers and participants who woke-up due to an alarm clock on days off, 159 glaucoma patients and 163 controls remained. Table 1 shows the characteristics of the study population. The group of glaucoma patients was older and consisted of fewer females, compared to the controls. Most of the patients had early glaucoma (63%); about one-third had either moderate (16%) or severe (21%) glaucoma in the better eye.

Table 2 presents the results from the MCTQ (A) and the corresponding calculated variables (B). The original questions (Table 2A) revealed no major differences in

average sleep timing parameters between the groups; however, for bedtime, time to get ready to fall asleep, sleep latency, minutes to get up after waking, and hours spent outside, the variability was larger in the glaucoma patients than in the controls. Figure 1 presents the distribution of chronotypes (MSF_{sc}). The mean and distribution of the MSF_{sc} were not significantly different between in glaucoma patients and controls (Table 2B; P=0.21 for mean and P=0.15 for variability). Table 3 shows the corresponding results after stratification to disease severity. The mean MSF_{sc} did not differ between the groups (P=0.62). The variability of chronotype showed a trend to increase with disease severity; the variability was significantly larger for the patients with severe glaucoma compared to the controls (P=0.023).

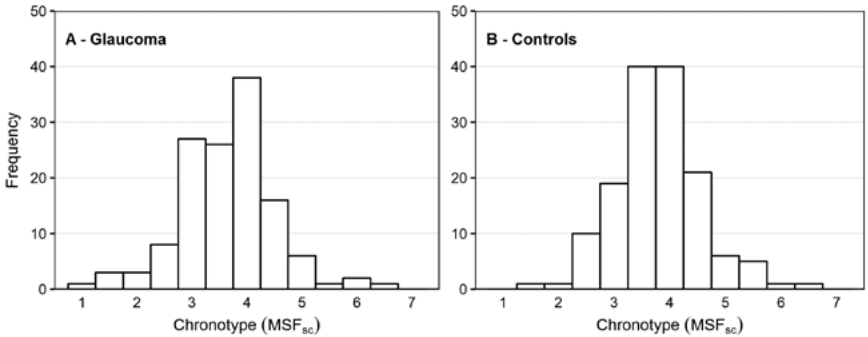

Figure 1. *Histogram with frequency as a function of chronotype (MSF_{sc}) for patients with glaucoma (A) and controls (B).*

Table 3. *MSF_{sc} mean and standard deviation as a function of disease severity.*

	n	MSF_{sc} mean	P value	MSF_{sc} SD	P value*
Controls	146	3:47	0.62	0:48	
Early glaucoma	88	3:40		0:49	0.40
Moderate glaucoma	21	3:45		0:55	0.20
Severe glaucoma	23	3:33		1:05	0.023

SD = standard deviation; * = compared to the controls.

DISCUSSION

Glaucoma does not affect the mean chronotype (MSF_{sc}). Chronotype variability increases with increasing disease severity.

The chronotype as a function of age in healthy subjects has been investigated in a large open study of around 25,000 subjects from Germany and Switzerland. In agreement with our study, the MSF_{sc} in subjects older than 50 years of age was between 3 and 4 AM, with a standard deviation of 1 hour.[24] Although chronotype was not assessed in glaucoma before, some studies that included glaucoma patients presented data on sleep timing. In agreement with our findings, they showed a general similarity between glaucoma patients and controls.[18,22,39] Albeit no differences in sleep timing, a lower sleep efficiency (the amount of actual sleep during the night) and quality have

been reported in glaucoma patients.[18–22] Of note, the previous studies did not analyze working days and days off separately. Since the sleep pattern on work days significantly differs from the sleep pattern on days off, the comparison to our study is limited.[23]

A limitation of the current study is that the glaucoma patients and controls significantly differed with respect to age and gender. However, the change of MSF_{sc} with age above 45 years of age is small, and gender differences also appear only significant below 45 years of age.[24] Therefore, age and gender differences between our groups are hardly relevant. Still, to confirm that age and gender differences did not influence the results, we adjusted the MSF_{sc} for age and gender and still did not find a difference between glaucoma patients and controls (P=0.91, t-test). A strength of this study is that we are the first that investigated chronotype as a measure of circadian phase in a large group of glaucoma patients and controls.

Our results did not show a delay in the mean MSF_{sc}, but did show an increase in variability of the MSF_{sc} for patients with severe glaucoma. These findings are in agreement with studies on the ipRGC-mediated pupil response, which has repeatedly been found to be similar in early glaucoma compared to healthy controls, while differences did appear in more advanced disease.[40–42] There are several hypotheses why there is no clear difference in chronotype distribution between early and moderate glaucoma patients and controls. First, it is not clear if the ipRGCs disappear in parallel with the image-forming RGCs, or only in advanced disease.[43–46] Second, a lower number of ipRGCs does not necessarily mean less effect – the dose-response curve may be highly nonlinear. A mouse study found that even with the loss of 83% of the ipRGCs, a normal ipRGC-mediated pupil constriction could still be obtained.4 Moreover, a hamster study reported that the circadian system attained saturation at lower irradiance levels than those required to induce pupil constriction.[47] Interestingly, the variability of the MSF_{sc} in patients with severe glaucoma did differ from that of the controls, indicating that some patients have more advanced and others more delayed sleep phases. The delay might be explained by the hypothesized change related to the longer than 24h intrinsic period. More advanced sleep phases may be explained by some people having an intrinsic period that is shorter than 24h and who at the same time suffer from a lack of delaying evening light or miss the acute effects of light keeping them awake.[11,48] An increase in artificial light and the adaptational properties of the non-image forming system might compensate for a change in the MSF_{sc}.[49,50] Whatever the mechanisms involved, individual shifts of the MSF_{sc} to either way will contribute to an increase in variability.

In conclusion, no significant difference is observed in the average chronotype as determined by sleep phase in patients with early or moderate glaucoma and healthy subjects. In severe glaucoma, chronotype variability seems to increase compared to healthy controls, but without a clear shift of the distribution. A more severe loss of ipRGCs in the human retina of glaucoma patients probably results in more difficulties with stable entrainment either due to a reduction in the phase shifting effects of light on the clock or to less influence of light on brain areas directly involved in sleep-wake regulation itself. Future studies might focus on a more in-depth analysis of the circadian clock in severe glaucoma and related disturbance of their quality of life.

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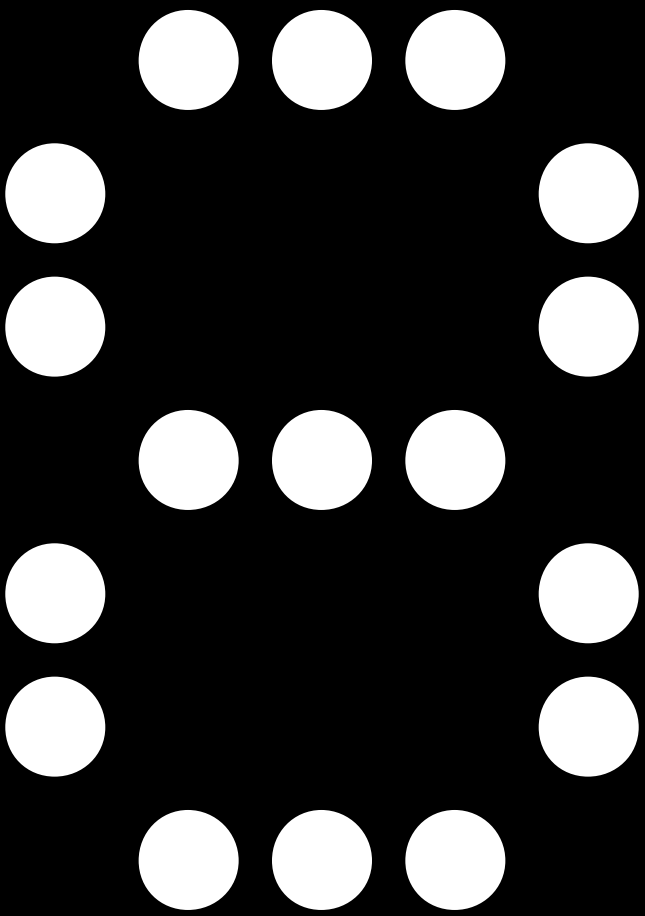

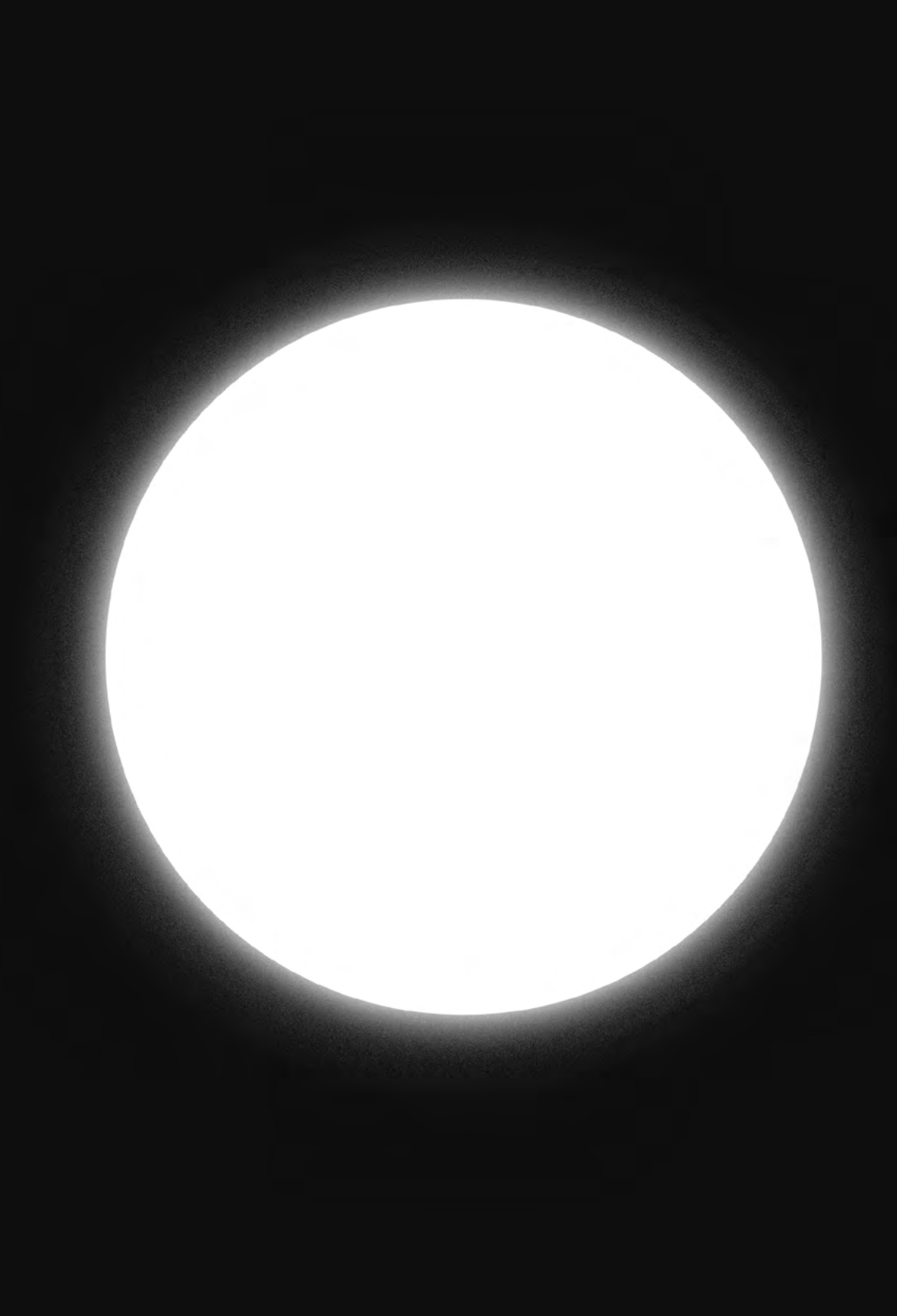

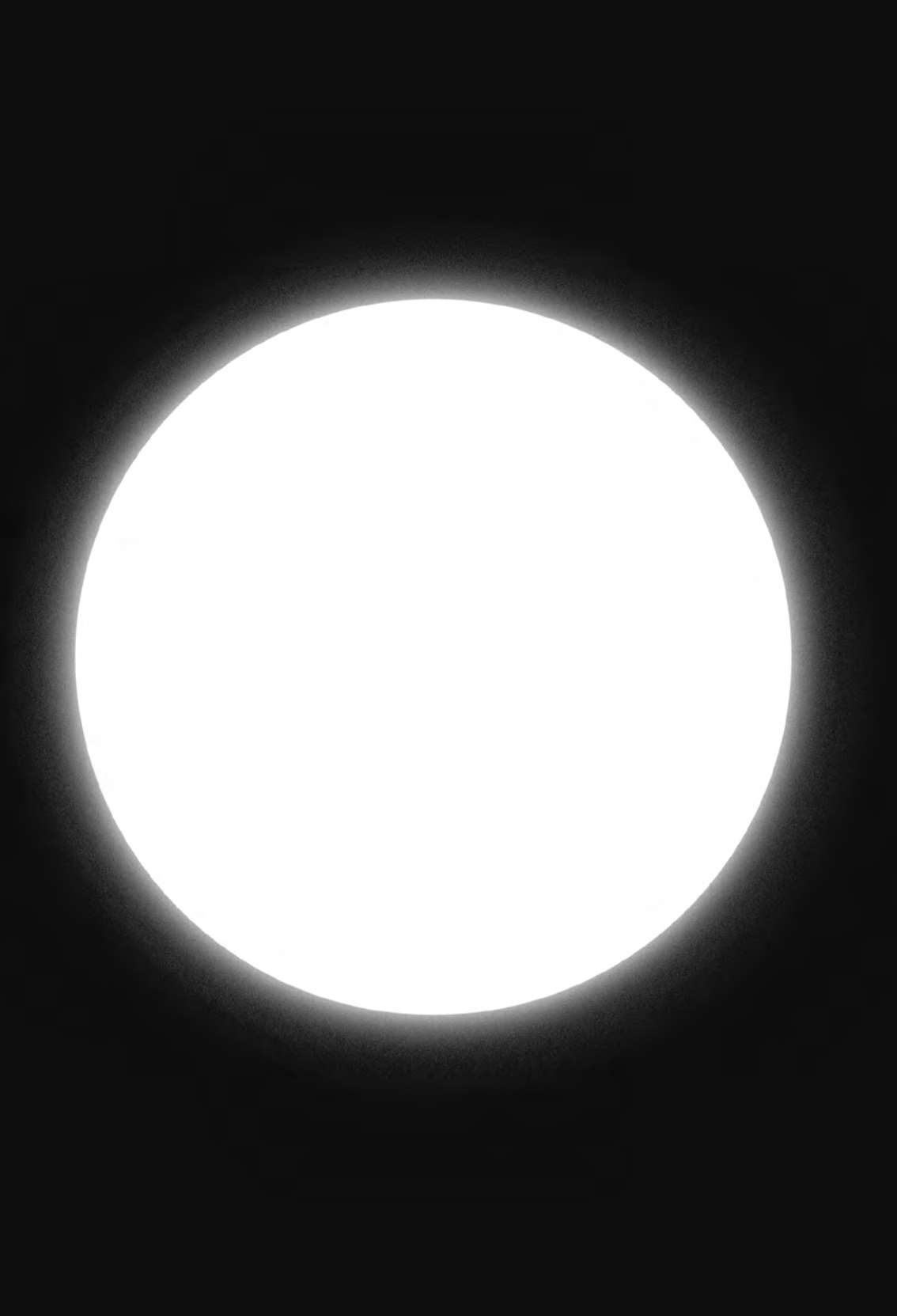

- SUMMARY &
  GENERAL DISCUSSION
- NEDERLANDSE SAMENVATTING
- CURRICULUM VITAE
- DANKWOORD

SUMMARY & GENERAL DISCUSSION

The objective of this thesis was to unravel the effect of luminance on visual functioning in glaucoma patients (Chapter 1). Therefore, we determined the effect of luminance on subjective (Chapter 2 and 6), and objective visual functioning (Chapter 3, 4 and 5). In addition, we explored the influence of glaucoma on the chronotype (Chapter 7). This general discussion will provide a summary of the chapters, connects subjective to objective visual functioning of glaucoma patients under different luminances, discusses the clinical implications of our findings, and provides recommendations for future research. Finally, the highlights of this thesis will be listed.

SUMMARY OF THE CHAPTERS

In **Chapter 1**, the background information and knowledge gaps were provided to appreciate how the two main themes of this thesis – glaucoma and light – come together in the objective. Glaucoma, physical quantities of light, light and dark adaptation, contrast sensitivity (CS) as a function of spatial frequency and luminance, and the available knowledge on visual functioning of glaucoma patients under extreme luminances were discussed as a prelude to this thesis.

In **Chapter 2**, the effect of luminance on *subjective* visual functioning in glaucoma was determined. We developed a luminance-specific questionnaire and asked a large group of glaucoma patients and controls to fill it out. We did not screen for the presence of other eye diseases but rather assumed that they would be equally distributed amongst both groups. As a consequence, we assumed that differences between the groups could specifically be attributed to glaucoma. The questions were addressing visual performance under five luminance conditions: presumed optimal (outdoor on a cloudy day), low, high, sudden decrease, and sudden increase. While the amount of visual complaints of the controls remained relatively low under all luminance conditions, glaucoma patients reported a strong increase of complaints towards extreme luminances, especially in the dark. With the best-differentiating question (concerning difficulties with seeing outside at night without moonlight), half of the glaucoma patients could be detected, without inducing many false-positives.

In **Chapter 3**, we took the first step to determine the effect of luminance on *objective* visual functioning in glaucoma. We aimed to determine whether three psychophysical laws (De Vries-Rose, Weber's, and Ferry-Porter's law) that hold in healthy subjects at different luminance ranges, are also applicable in glaucoma patients. Therefore, we measured the CS using Weber contrast, and the frequency at which a flickering stimulus becomes perceived as steady (critical fusion frequency; CFF) at different luminance levels. All three psychophysical laws were applicable to glaucoma patients. However, even in apparently intact areas of the visual field, the CS and CFF was lower in glaucoma patients, without a clear luminance dependency that was consistent across the various experiments.

In **Chapter 4**, we described our second experiment to determine the effect of luminance on *objective* visual functioning in glaucoma. In contrast to Chapter 3, we considered the spatial frequency and increased the maximum luminance to cover all luminances that can be experienced in daily life. We measured the CS using Michelson contrast, over a very wide range of luminances (from star- to sunlight). Since measurements at such high luminances have never been performed in healthy subjects, the findings in controls were of great interest already. In controls, Weber's law held at 3 and 10 cpd. However at 1 cpd, their logCS decreased for the extremely high luminances, which is in disagreement with Weber's law. At 1 and 10 cpd, the results for glaucoma patients and controls were similar. However, at 3 cpd, the CS was lower in glaucoma patients, with the greatest difference to the controls at lower luminances.

In **Chapter 5**, we described our third experiment to determine the effect of luminance on *objective* visual functioning in glaucoma. We now focused on the adaptation process, rather than the adapted visual system, as we did in Chapter 3 and 4. Following a sudden increase and decrease in luminance, we measured the CS using Weber contrast as a function of time. For both light and dark adaptation, we found that – compared to controls – glaucoma patients had a lower CS at all time points, yet showed similar adaptation times.

In **Chapter 6**, we determined the effect of luminance on *subjective* visual functioning, in real-life environments after dark. We recruited a citizen science network of smartphone users with and without an eye disease who – by means of an app – reported their visual complaints when walking outside after dark. At the same time, they measured the corresponding amount of light reflected by the pavement. For participants with healthy eyes, complaints increased especially below luminances of 0.01 cd/m^2, while for those with an eye disease (including glaucoma), the increase started already at a luminance level four times higher than that.

In **Chapter 7**, we explored whether glaucoma also affects nonvisual responses to light, such as the sleep-wake cycle. In healthy subjects, the circadian clock is entrained to light by the input of a special type of RGCs: the intrinsically photosensitive RGCs (ipRGCs). Loss of ipRGCs in glaucoma patients might result in a lower susceptibility of the circadian clock to light and a change in the sleep-wake cycle. Therefore, we compared the chronotype (the midpoint between sleep onset and wake-up time on days off) as a measure of circadian phase between glaucoma patients and healthy subjects. We found no difference in the average chronotype in patients with early or moderate glaucoma and controls. In severe glaucoma, chronotype variability seemed to increase compared to controls, but without a clear shift in the distribution. This indicates that some patients may advance and others delay their sleep phase with increasing glaucoma severity.

GENERAL DISCUSSION

The main objective of this thesis was to unravel the effect of luminance on visual functioning in glaucoma patients. Therefore, we determined the effect of luminance on (1) subjective and (2) objective visual functioning in glaucoma. These two aims will be discussed and related below.

1. The effect of luminance on subjective visual functioning in glaucoma

Although glaucoma patients are considered to be asymptomatic, fragmentary findings revealed that they seem to experience visual difficulties under extreme (low, high, or rapidly changing) luminance conditions.[1–6] In Chapter 2, we confirmed that differences in visual complaints between glaucoma patients and controls are small with optimal luminance, but quite pronounced under extreme luminance conditions. The low luminance condition discriminated best, and luminance-specific complaints were more frequent with increasing disease severity. Therefore, the widely accepted concept of glaucoma as an asymptomatic disease is only valid with optimal luminance. We can conclude that visual complaints under extreme luminances, especially in the dark, are a symptom of (early-stage) glaucoma.

2. The effect of luminance on objective visual functioning in glaucoma

Studies regarding the effect of luminance on objective visual functioning in glaucoma have been very scarce. In Chapters 3, 4, and 5, we laid the foundation for this field of research. Figure 1 represents the visual function (logCS) as a function of luminance for the results reported in Chapters 3 and 4. We found that glaucoma patients had a lower objective visual function without a clear luminance dependency that is consistent across the various experiments. In other words, the curve of the glaucoma patients is shifted downwards compared to that of the controls. This indicates an impaired signal processing downstream in the retina and beyond, rather than an impaired light and dark adaptation in the strictest sense (rod and cone function). The latter is in agreement with the results from the traditional light and dark adaptation experiment reported on in Chapter 5, where we did not find a difference in adaptation times between glaucoma patients and controls. Although the studies in this thesis did not investigate the nature of the impaired signal processing, we did attempt to relate it to the CS and CFF at different luminances (Chapter 3). However, psychophysics does not allow for definitive conclusions about the anatomic location of these processes.[7]

3. Connecting subjective to objective visual functioning

Glaucoma patients have a much worse subjective impression of their vision under extreme luminances compared to healthy subjects. However, the objective difference in function did not result in a clear luminance dependency that is consistent across the various experiments. For vision at low luminances and during dark adaptation, this discrepancy might be explained by a certain minimum amount of function needed for acceptable vision (the horizontal dotted line in Fig. 1). When going from twilight to starlight, glaucoma patients will fall below this minimum amount of function (e.g., CS) earlier than healthy subjects; when adapting to darkness, glaucoma patients take longer to reach it. From this point on, this concept will be referred to as the minimum visual function hypothesis.

In Chapter 6, we related visual complaints when walking after dark to the corresponding luminance of the pavement. In line with the minimum visual function hypothesis, while participants without an eye disease had a modest increase in complaints towards the lowest luminances below 0.01 cd/m^2, the increase in visual

complaints in participants with an eye disease (including glaucoma patients) started already at 0.04 cd/m^2. To estimate the minimum CS needed to walk after dark without complaints, we took the logCS of glaucoma patients from Chapter 3 at 0.04 cd/m^2. For the central and the best-preserved peripheral visual field, this logCS was about 0.3. In other words, visual complaints when walking after dark might arise when we can no longer distinguish small objects with a luminance that differs by 50% from the pavement. Obviously, other values may be needed for performing more complex tasks.

Although the minimum visual function hypothesis offers an explanation for visual complaints of glaucoma patients under low luminances and during dark adaptation, it does not offer an explanation for visual complaints under high luminances. The CS and CFF of glaucoma patients do not decrease towards higher luminances (Chapter 3 and 4). Therefore, the reason why glaucoma patients experience more complaints under extremely high luminances (Chapter 2) remains unknown. Because light adaptation in both glaucoma patients and controls was very fast, we were not able to determine potential differences in light adaptation times (Chapter 5). Therefore, the increase in complaints during light adaptation (Chapter 2) also remains unsolved. However, since visual complaints in glaucoma patients are most pronounced in the dark (Chapter 2), an explanation (and solution) for complaints at low luminances seems the most relevant from the patient's perspective.

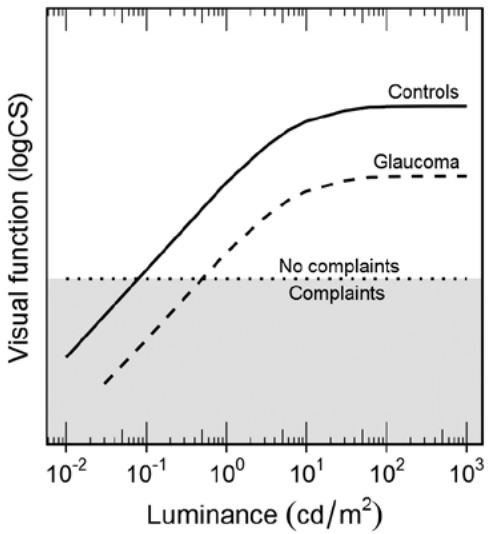

Figure 1. *Visual function (logCS) as a function of luminance for the results found in Chapter 3 and 4. Glaucoma patients had a lower objective visual function without a clear luminance dependency. A minimum visual function needed for acceptable vision (the horizontal dotted line) might explain more frequent complaints of glaucoma patients in and when adapting to the dark.*

CLINICAL IMPLICATIONS

Medical doctors are trained in the believe that glaucoma, especially at an early stage, is an asymptomatic disease. Based on the research presented in this thesis, it should be clear that this is not the case: visual complaints under extreme (low, high, or rapidly changing) luminances, especially in the dark, are a symptom of glaucoma (Chapter 2). The next question is whether we could benefit from this finding in terms of screening, diagnostics or rehabilitation.

From the point of preventing blindness, moderate and severe glaucoma are the most important stages to detect.[8,9] Reported complaint frequencies in response to the question 'How much difficulty do you experience with seeing outside at night when there is no moonlight?' corresponded to a sensitivity of 74% for these glaucoma stages, at a specificity of 94% (Chapter 2). This implies – by definition – that 3 out of 4 patients with moderate/severe glaucoma will be identified correctly. With a prevalence of glaucoma of 2% in the general elderly population, this results in a positive predictive value of 20% and negative predictive value of more than 99%. Therefore, by simply asking one question, we can increase the likelihood of someone having glaucoma from one out of fifty (prevalence), to one out of five. Hence, this could be a first step in screening for glaucoma in the population.

For actual diagnostics, we seem to be on track with our current methods. The difference between glaucoma patients and controls was larger when presenting a small stimulus as used in static perimetry (Chapter 3), instead of a larger stimulus with sine-wave gratings (Chapter 4). In addition, there was not a clear luminance dependency of the difference between glaucoma patients and controls. Therefore, the follow-up of glaucoma patients with perimetry that measures the CS using Weber contrast with a small stimulus of 0.43° at 10 cd/m^2, seems to be a decent choice.

From a rehabilitation point of view, at low luminances, glaucoma patients need approximately 3 to 10 times higher luminances than healthy subjects in order to have the same visual function (Fig. 1; Chapter 3 and 4). Therefore, the advice to increase the luminance to decrease visual complaints seems justified. However, the increase of visual function with luminance is not infinite. At high luminances, glaucoma patients still have a lower visual function than healthy subjects, which cannot be compensated for by a further increase in luminance (Fig. 1; Chapter 3 and 4).

RECOMMENDATIONS FOR FURTHER RESEARCH

Subjective visual functioning in glaucoma

- The question 'How much difficulty do you experience with seeing outside at night when there is no moonlight?' resulted in remarkably high sensitivity and specificity of 48% and 94%, respectively (Chapter 2). Replication of this finding and determining its value for screening in population-based studies is a logical next step.

Objective visual functioning in glaucoma

- Generally, the difference in objective visual functioning did not show a clear luminance dependency that was consistent over the experiments (Chapter 3 and 4). However, while the Ferry-Porter law did apply to glaucoma patients, its slope was smaller in glaucoma patients than in controls (Chapter 3). This implies a greater difference in CFF between the groups under extremely high luminances, which may be helpful in glaucoma diagnostics. To explore this further, an experimental setup could be constructed that is variable for stimulus size, temporal characteristics, and position, with a high maximum luminance.
- We found larger differences between glaucoma patients and controls using small and/or flickering stimuli (Chapter 3), than using large, static stimuli (Chapter 4). Since redundancy in the latter stimuli might be the explanation, future studies should avoid large static stimuli for glaucoma diagnostics. Nevertheless, it might be worth to confirm the striking difference with a large 1 cpd stimulus at 1 cd/m^2 (Chapter 4).
- We did not find an explanation for the visual complaints of glaucoma patients under high luminance or during light adaptation (Chapter 8). Obviously, there might be additional objective visual functions than just CS and CFF that are impaired in glaucoma patients, and that may be influenced by luminance. A promising direction of research could be motion perception.[10,11] In addition, the visual function under continuously changing background luminances over a much smaller range than in Chapter 5 may be more applicable to daily life than the visual function at one uniform background luminance.

Citizen science

- Citizen science projects can be useful when investigating health issues of the population in relation to the environment (Chapter 6). Moreover, the technology that is offered by tablets and smartphones might even enable screening or follow-up of diseases in the foreseeable future. Despite the high potential, medical citizen science projects are still rare compared to other disciplines.[12] Due to the fast increase in the number of elderly in the upcoming decades, self-reliance facilitated by technology will probably be necessary to unburden our healthcare system.

Chronobiology

- Our study to the chronotype of glaucoma patients can be considered a first exploration. Since chronotype variability seemed to increase with increasing disease severity, future studies might focus on a more in-depth analysis of the circadian clock in severe glaucoma and related disturbances to their quality of life.

HIGHLIGHTS

- Glaucoma is only asymptomatic with optimal luminance (Chapter 2).
- Visual complaints in the dark are a symptom of early-stage glaucoma (Chapter 2).

- At low luminances, glaucoma patients need approximately 3 to 10 times more luminance than healthy subjects in order to have the same visual function (Chapter 3 and 4).
- At high luminances, glaucoma patients still have a lower visual function than healthy subjects, which cannot be compensated for by a further increase in luminance (Chapter 3 and 4).
- Glaucoma patients do not have longer dark adaptation times (Chapter 5).
- When going from twilight to starlight, subjects with an eye disease experience complaints earlier than subjects without an eye disease (Chapter 6).
- A minimum visual function needed for acceptable vision might explain why glaucoma patients have more frequent complaints in and when adapting to the dark (Chapter 2, 3, 4, 5, and 6).
- Glaucoma might also have an influence on nonvisual responses to light such as the sleep-wake cycle (Chapter 7).

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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
BCVA	Best-corrected visual acuity
cd/m^2	Candela per square meter
CFF	Critical fusion frequency
CI	Confidence interval
cpd	Cycles per degree
CS	Contrast sensitivity
CSF	Contrast sensitivity function
dB	Decibel
FDT	Frequency doubling technology
GLGS	Groningen Longitudinal Glaucoma Study
HFA	Humphrey Field Analyzer
IOP	Intraocular pressure
ipRGCs	Intrinsically photosensitive retinal ganglion cells
IQR	Interquartile range
logCS	Logarithm of the contrast sensitivity
logMAR	Logarithm of the minimum angle of resolution
M	Missing
MCTQ	Munich ChronoType Questionnaire
MD	Mean deviation
METc	Medical ethical committee
MSF	Mid-sleep on days off
MSF_{sc}	Mid-sleep on days off corrected for workweek accumulated sleep debt
N	Number
NA	Not applicable
ND	Neutral density
OR	Odds ratio
POAG	Primary open angle glaucoma
RGCs	Retinal ganglion cells
RNFL	Retinal nerve fiber layer
SAP	Standard automated perimetry
SD	Standard deviation
SF	Spatial frequency
Td	Troland
TSTI	Three-step test-interview
UMCG	University Medical Center Groningen

NEDERLANDSE SAMENVATTING

Het gezichtsvermogen is een van de belangrijkste zintuigen om aan het dagelijks leven deel te nemen. Met het verminderen van het gezichtsvermogen wordt deelname aan de maatschappij beperkt en vermindert ook de kwaliteit van leven. Oogziekten zoals glaucoom komen vaak voor bij ouderen. Door de vergrijzing zal het aantal ouderen in de westerse wereld de komende decennia verdubbelen. Daarmee verdubbelt ook het aantal patiënten met een oogziekte. Het investeren in onderzoek naar oogziekten en de wijze waarop oogheelkundige patiënten zich in hun omgeving voortbewegen is daarom essentieel.

Deze Nederlandse samenvatting geeft een overzicht van dit proefschrift en kan los gelezen worden van de andere hoofdstukken. In de **Introductie** zal worden uitgelegd wat het doel is van dit proefschrift. Daarna zal in de **Samenvatting van de hoofdstukken** worden uitgelegd wat we hebben onderzocht. Ten slotte zal in de **Discussie** worden beschreven wat dit proefschrift bijdraagt aan de al bestaande kennis.

INTRODUCTIE

Zien begint met licht dat door het hoornvlies, de pupil, de lens en het glasvocht gaat, om uiteindelijk op het netvlies terecht te komen. De lichtgevoelige cellen (staafjes en kegeltjes) in het netvlies zetten licht om in een elektrisch signaal, dat via de oogzenuw naar de hersenen wordt gebracht. Nadat het signaal is verwerkt en geïnterpreteerd, vormen de hersenen het beeld dat we zien van de buitenwereld. Glaucoom is een chronische en progressieve oogziekte waarbij de oogzenuw wordt beschadigd. Dit uit zich in het verlies van gedeelten in het gezichtsveld. Gezichtsveldverlies bij glaucoom start typisch aan de buitenkant en ontwikkelt zich langzaam naar meer centrale gedeelten. Glaucoom komt voor bij 2% van de bevolking en is de meest voorkomende oorzaak van onomkeerbare blindheid in de wereld. De grootste risicofactor voor glaucoom is een verhoogde oogdruk; de combinatie van een verdacht uitziende oogzenuw en gemeten gezichtsveldverlies bevestigt de diagnose. Het verlagen van de oogdruk met oogdruppels, laserbehandeling of operatie is de enige effectieve behandeling.

Vroege detectie van glaucoom is cruciaal doordat schade aan de oogzenuw en het gezichtsveld niet ongedaan gemaakt kan worden. Echter, het ziekteverloop is verraderlijk doordat patiënten een verhoogde oogdruk niet kunnen voelen en gezichtsveldverlies van één oog kan worden gecompenseerd door informatie uit het andere oog. Daarnaast vult het brein missende gedeelten in het gezichtsveld van beide ogen slim in. Om deze redenen wordt glaucoom, althans in het begin van de ziekte, gezien als asymptomatische ziekte (een ziekte zonder klachten) en zit er vaak een lange tijd tussen het ontstaan van glaucoom en de gang naar de dokter. Het is echter de vraag of glaucoom daadwerkelijk volledig asymptomatisch is, of dat we bepaalde symptomen nog niet hebben herkend als passend bij de ziekte.

Tijdens het oogheelkundige spreekuur benoemden glaucoompatiënten moeilijk zien onder extreme (lage, hoge en snel wisselende) lichtomstandigheden als symptoom voor hun ziekte. *Het doel van dit proefschrift was daarom om te ontrafelen wat het effect is van licht op het visueel functioneren van glaucoompatiënten.*

SAMENVATTING VAN DE HOOFDSTUKKEN

In **hoofdstuk 1** werd de basis gelegd voor het begrijpen van de relevantie en de experimenten in dit proefschrift.

In **hoofdstuk 2** hebben we met een nieuw ontworpen vragenlijst onderzocht of glaucoompatiënten daadwerkelijk meer moeite hebben met zien onder extreme lichtomstandigheden. De vragen in de vragenlijst gingen over het visueel functioneren onder vijf omstandigheden: bij optimaal licht (buiten op een bewolkte dag), in het donker, in het felle licht, en bij een plotselinge toename of afname van de hoeveelheid licht. Mensen zonder glaucoom bleken relatief weinig klachten te hebben onder optimale en extreme lichtomstandigheden. Glaucoompatiënten hadden ook weinig klachten onder optimale omstandigheden, maar veel klachten onder extreme lichtomstandigheden. De meeste klachten van glaucoompatiënten betroffen het zien in het donker. Met de vraag 'Heeft u door uw gezichtsvermogen moeite met buiten zien 's nachts zonder maanlicht' konden we verrassend goed glaucoompatiënten van mensen zonder glaucoom onderscheiden.

Nu we hadden aangetoond dat glaucoompatiënten daadwerkelijk veel moeite ervaren met zien onder extreme lichtomstandigheden, wilden we onderzoeken of dit ook objectief vastgelegd kon worden. De waarneming van mensen met gezonde ogen bij lage en hoge lichtomstandigheden gaat volgens een vast patroon. Dit patroon stelt dat de visuele functie beter wordt naarmate er gemeten wordt bij meer licht, tot een bepaalde hoeveelheid. Als er voldoende licht is, dan blijft de visuele functie gelijk, ook als de hoeveelheid licht nog verder toeneemt.

In **hoofdstuk 3** hebben we onderzocht of het hierboven beschreven patroon dat geldt voor mensen met gezonde ogen, ook geldt voor glaucoompatiënten. Hiervoor werd de contrastgevoeligheid (het vermogen kleine verschillen in helderheden waar te nemen) en de kritische fusie frequentie (de frequentie waarop knipperend licht wordt waargenomen als continu) gemeten. De lichtomstandigheden werden gevarieerd van laag tot middelhoog door gebruik te maken van brillen met lichtfilters. Voor glaucoompatiënten bleken dezelfde patronen te gelden als voor mensen met gezonde ogen. Echter, de contrastgevoeligheid en de kritische fusie frequentie van glaucoompatiënten was onder alle lichtomstandigheden een stuk lager dan die van mensen met gezonde ogen.

Het bereiken van lage lichtomstandigheden is eenvoudig door het gebruik van lichtfilters. Voor hoge lichtomstandigheden zijn we echter gebonden aan de maximale hoeveelheid licht die de opstelling (meestal een computerscherm) kan aanbieden. In **hoofdstuk 4** werd door middel van een beamer en een doorkijkscherm een nieuwe opstelling gebouwd om de maximale hoeveelheid licht te kunnen verhogen. In het experiment werd de contrastgevoeligheid gemeten van lage tot extreem hoge lichtomstandigheden

(van sterren- tot zonlicht). Volgens het hierboven beschreven vaste patroon zou de visuele functie richting extreem hoge lichtomstandigheden gelijk moeten blijven. Verrassend was dat de visuele functie voor mensen met gezonde ogen hier juist afnam. Daarnaast vonden we opnieuw dat de contrastgevoeligheid van glaucoompatiënten onder alle lichtomstandigheden lager was dan die van mensen met gezonde ogen.

In de hoofdstukken 3 en 4 werd de visuele functie gemeten nadat de proefpersonen tijd hadden gehad om zich aan te passen aan een nieuwe lichtomstandigheid. In **hoofdstuk 5** werd juist dit aanpassingsproces in kaart gebracht: de licht- en donkeradaptatie. Hierbij werd na een plotselinge toe- of afname van de hoeveelheid licht, de contrastgevoeligheid in de loop van de tijd gemeten. Glaucoompatiënten en mensen met gezonde ogen hadden dezelfde tijd nodig om aan te passen aan een nieuwe lichthoeveelheid, al bleef de contrastgevoeligheid van glaucoompatiënten op alle tijdspunten onder die van mensen met gezonde ogen.

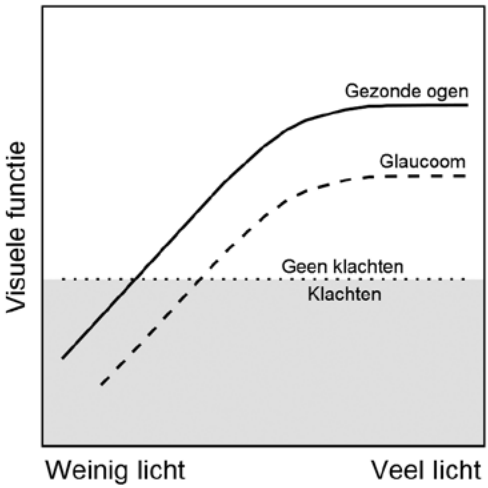
Hoofdstuk 6 beschrijft het publieksonderzoek 'Zicht op Licht' waarin we de relatie onderzochten tussen de hoeveelheid licht 's nachts in Nederland en de moeite met zien. Deelnemers gingen 's avonds na zonsondergang de straat op om met hun smartphone de hoeveelheid licht die vanaf de ondergrond komt te meten. Tegelijkertijd gaven zij aan hoeveel moeite ze hadden met zien om zich voort te kunnen bewegen. In totaal werden bijna 7000 metingen verzameld. Het percentage van de deelnemers met gezonde ogen dat moeite had met zien nam toe richting extreem lage lichtomstandigheden. Echter, het percentage van de deelnemers met een oogziekte dat moeite had met zien nam al toe bij vier keer zoveel licht. Met andere woorden, naarmate het donkerder werd ervoeren deelnemers met een oogziekte eerder moeite met zien dan deelnemers met gezonde ogen.

Naast dat we licht nodig hebben om te zien, heeft licht ook een invloed op niet-visuele systemen, zoals het slaap-waak ritme. In **hoofdstuk 7** onderzochten we de invloed van glaucoom op het slaap-waak ritme. Bij mensen is het slaap-waak ritme afhankelijk van de hoeveelheid licht dat via de ogen binnenkomt. Bij glaucoompatiënten is dit systeem mogelijk verstoord waardoor er een verschuiving van dit ritme kan plaatsvinden. Voor patiënten met weinig tot matig glaucoom bleef het slaap-waak ritme gelijk aan mensen met gezonde ogen. Bij patiënten met ernstig glaucoom was het slaap-waak ritme bij sommigen naar voren geschoven, terwijl anderen een verlaat ritme lieten zien.

DISCUSSIE

Het doel van dit proefschrift was om te ontrafelen wat het effect is van licht op het visueel functioneren van glaucoompatiënten. Glaucoompatiënten bleken veel meer klachten te ervaren onder extreme (hoge, lage en snel wisselende) lichtomstandigheden dan mensen met gezonde ogen, en dan met name in het donker. Veel moeite met zien in het donker kan daarom gezien worden als een symptoom voor glaucoom. Figuur 1 laat een typisch resultaat zien van het onderzoek uit dit proefschrift. De visuele functie wordt beter naarmate er bij meer licht wordt gemeten (van links naar rechts in de grafiek), tot een bepaalde hoeveelheid. Vanaf dat punt blijft de visuele functie gelijk, ook als de hoeveelheid licht nog verder toeneemt. Doordat de curve van glaucoompatiënten naar

beneden is verschoven kunnen we concluderen dat glaucoompatiënten onder alle lichtomstandigheden een slechtere visuele functie hebben dan mensen met gezonde ogen. Visuele functie en klachten kunnen aan elkaar gekoppeld worden door een minimale hoeveelheid functie die nodig is om te zien zonder klachten (de horizontale stippellijn). Als het vanuit het licht steeds donkerder wordt (van rechts naar links in de grafiek), dan zullen glaucoompatiënten eerder het punt bereiken waarop ze klachten ervaren dan mensen met gezonde ogen. Dit verklaart waarom glaucoompatiënten veel moeite hebben met zien in het donker. Bij weinig licht (links in de grafiek) hebben glaucoompatiënten voor dezelfde visuele functie als mensen met gezonde ogen meer licht nodig. Bij veel licht (rechts in de grafiek) hebben glaucoompatiënten nog steeds een slechtere visuele functie dan mensen met gezonde ogen, alleen kan dit niet gecompenseerd worden door meer licht. Hoewel glaucoompatiënten dus ook bij goed licht een slechtere visuele functie hebben, is die – zo blijkt uit ons onderzoek – kennelijk wel voldoende om (grotendeels) klachtenvrij te zijn.



Figuur 1. *De visuele functie uitgezet tegen de hoeveelheid licht. Glaucoompatiënten hebben bij alle lichtomstandigheden een lagere visuele functie dan mensen met gezonde ogen. Een minimale visuele functie die nodig is om te zien zonder klachten (de horizontale stippellijn) verklaart waarom glaucoompatiënten moeite hebben met zien in het donker.*

Samengevat, het concept van glaucoom als een asymptomatische ziekte geldt alleen als het licht optimaal is. Veel moeite met zien in extreme lichtomstandigheden, met name in het donker, is een symptoom voor glaucoom. De visuele functie van glaucoompatiënten is voor alle lichtomstandigheden lager dan die van mensen met gezonde ogen. Hierdoor zullen glaucoompatiënten als het donker wordt eerder het punt bereiken waarop ze klachten ervaren dan mensen zonder glaucoom.

CURRICULUM VITAE

Ronald Augustinus Joseph Maria Bierings (Tilburg, 1987) is a medical doctor and researcher with a passion for Physics and Education. After graduating cum laude from his secondary school in 2005, he studied Applied Physics at Eindhoven University of Technology. After two years, he decided to change his path and started studying Medicine at Utrecht University. During his studies, he gained extracurricular experience in nursing care and served internships in developing countries in Asia and Africa. Additionally, he was trained as physics teacher and trainer of new teachers, to help secondary school students prepare for their exams at Leiden University. In 2014 he obtained his Master's degree in Medicine, and applied for a PhD position at the Laboratory of Experimental Ophthalmology of the University Medical Center Groningen. His PhD project provided him with the opportunity to combine Medicine, Physics, and Education. In 2015, his research proposal 'Zicht op Licht' was awarded as the citizen science project of the National Science Weekend in the Netherlands. During his PhD period, his free time was filled with music, as trumpet player in the Peggy Bouwer Jazz Quartet and concert band Gruno's Postharmonie Groningen. On Remembrance Day 2017, he served as taptoe trumpeter of the city of Groningen. After having obtained his PhD degree, Ronald will continue his career as medical doctor at the department of Neurology of the Reinier de Graaf Gasthuis in Delft. In 2019, he will start as resident in training for Neurologist at Leiden University Medical Center.

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