INSIGHT IN TO LIGHT

The influence of luminance on visual functioning in glaucoma

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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.

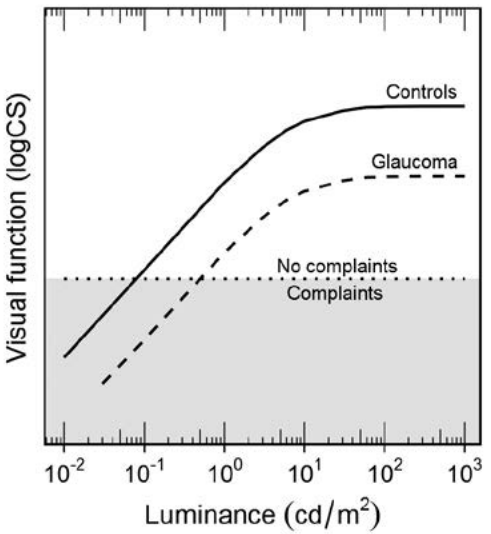

Figure 1. *Visual function (logCS) as a function of luminance for the results found in Chapter 3 and 4. Glaucoma patients had a lower objective visual function without a clear luminance dependency. A minimum visual function needed for acceptable vision (the horizontal dotted line) might explain more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