**Article**

# Contrast-to-Noise Ratios for Assessing the Detection of Progression in the Various Stages of Glaucoma

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**Purpose:** We determine the contrast-to-noise ratios (CNRs) of structural and functional measurements to assess their sensitivity to detect progression in the various stages of glaucoma.

**Methods:** We calculated the CNRs for the mean peripapillary retinal nerve fiber layer (RNFL) thickness measured by spectral domain optical coherence tomography, and the mean deviation (MD) and visual field index (VFI) determined by standard automated perimetry for the transitions between five stages. Longitudinal data from healthy and glaucomatous eyes from a prospective study were used. Contrast was defined as the change in the mean value of the parameter between two successive stages. Noise was defined as the variability of the parameter and calculated from the residuals of linear regression on the data from five subsequent visits per eye.

**Results:** We studied 205 eyes from 125 participants (46% men, 54% women). CNRs for different parameters varied considerably across the range of disease severity (0.8–12.2). The RNFL thickness had a higher CNR in the transition from normal to mild glaucoma (12.2) compared to the CNRs of the functional measures (MD 4.1, VFI 4.5). The CNRs for the functional measures were higher in the transition from moderate to advanced (MD 5.2, VFI 5.8) and advanced to severe glaucoma (MD 7.2, VFI 5.8) compared to the RNFL thickness (CNR 0.8 and 3.2, respectively).

**Conclusions:** The RNFL thickness is more sensitive for detecting glaucomatous progression at the onset of glaucoma compared to the functional measures, while the latter are more sensitive for detecting progression in the later stages of glaucoma.

**Translational Relevance:** The CNR method can be used to determine which measurement is most sensitive for detecting progression in glaucoma, differentiated for the severity of the disease. Furthermore, it creates a basic toolset for determining the most sensitive measurement in detecting progression not only in glaucoma, but other (ophthalmic) diseases as well.

## Introduction

Glaucoma is the second leading cause of blindness in the world according to the World Health Organization, with an estimate of over 60 million people affected worldwide.[1,2] It is a progressive optic neuropathy that, if untreated, leads to irreversible loss of retinal ganglion cells and thinning of the retinal nerve fiber layer (RNFL) before visual field (VF) loss.[3] Therefore, early detection of progression is essential for preventing further VF loss.[4]

Glaucomatous progression can be assessed by structural testing, such as measuring the peripapillary RNFL thickness with spectral domain optical coherence tomography (SD-OCT)[5–7] and/or functional testing with perimetry (VF testing). However, the correlation between these two types of measurements generally is poor. Several studies have presented cases where structural changes were seen in the RNFL while no functional changes were detected and vice versa.[8–12] One possible explanation for this poor correlation between different measurement techniques

is their measurement variability. Any progression is more difficult to detect with greater measurement variability.[13]

It has been suggested that structural tests are better used in early stages of glaucoma for the detection of progression, whereas functional measurements are better used in more advanced stages.[10,14–18] We would argue, however, that it is not possible to directly compare the different types of measurements, structural and functional, because they are expressed in different units of measure. Therefore, a dimensionless measure is needed to make this comparison possible as to determine which type of measurement or which parameter (e.g., mean deviation [MD] or visual field index [VFI] for perimetry or mean RNFL thickness for OCT) is actually the most sensitive for the detection of glaucomatous progression.

By using contrast-to-noise ratios (CNRs), the comparison between structural and functional measurements in their capacity to detect change can be made possible.[19] The CNR equals the ratio of the difference in magnitude between measurements in successive stages (i.e., contrast) and the reproducibility of the measurement (i.e., noise). We determine the contrast from cross-sectional measurements at different stages of the disease, while the noise was assessed from annual follow-up measurements. The higher the CNR, the more levels between two stages can be discriminated.

We used the CNR method to determine the sensitivity of different types of measurements for detecting glaucomatous progression. We calculated the CNRs of the MD and VFI measured by standard automated perimetry (SAP; functional) and peripapillary RNFL thickness measured by SD-OCT (structural). We then compared these CNRs to determine which of these measurements is most sensitive for detecting progression in glaucoma at various stages of the disease.

## Methods

Data from participants in the Rotterdam Glaucoma Imaging Study (GIS) were used for the current analysis. GIS is a prospective, longitudinal study in which both eyes of glaucoma patients and healthy volunteers are measured regularly with various kinds of measurement techniques that are used commonly in the clinical management of glaucoma. The study is designed to evaluate the functional and structural measurements for the detection and monitoring of glaucoma. For inclusion, healthy subjects were required to have an intraocular pressure of ≤22 mm Hg and a normal VF, defined as a Glaucoma Hemifield Test (GHT) within normal limits and an MD and pattern standard deviation (PSD) within the normal range. Glaucoma patients were included if their VF defects were reproducible on at least one occasion and if at least two of the following findings on the successive VF were confirmed: a PSD significant at the 5% probability level, a GHT outside normal limits, and a cluster of ≥3 points below the 5% probability level or 1 individual point below the 1% probability level. Eyes were excluded from participation in the presence of any coexisting ocular or systemic disease known to possibly affect the VF (e.g., diabetes mellitus), a history of intraocular surgery (except for uncomplicated cataract surgery or glaucoma surgery), uncontrolled arterial hypertension, and secondary glaucoma, except pigmentary. All participating eyes had a best corrected Snellen visual acuity of at least 20/40, a spherical equivalent refractive error between −10.0 and +5.0 diopters (D), and unremarkable findings upon slit-lamp examination, including open angles on gonioscopy. The study was approved by the medical ethics committee of the Erasmus Medical Center and complies with the Declaration of Helsinki. Written informed consent was obtained from all participants.

The five most recent eligible visits per eye were used in the current analysis. To be included in the analysis, a Spectralis OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) peripapillary circle scan and a Humphrey Field Analyzer (II-i Series; Carl Zeiss Meditec, Inc., Dublin, CA) VF examination needed to be performed on the same day. OCT circle scans consisted of a single B-scan (796 A-scans) centered on the optic nerve head (circle diameter 3.5 mm) that was averaged from 16 B-scans by the device's automatic real-time tracking (ART). OCT scans with an image quality <15 dB, incomplete scans, or scans that were deemed unsuitable for analysis by the operator of the Glaucoma Imaging Study due to segmentation errors were excluded. VF tests were performed with the 24-2 SITA Standard test algorithm. VFs were required to have false-positive or false-negative values <15% and fixation losses <15% for inclusion in the analysis. In case of advanced or severe glaucomatous VF damage, false-negative values ≥15% were accepted. In total, 38 glaucomatous eyes of 27 glaucoma patients, and 20 healthy eyes of 13 healthy patients were excluded from analysis due to poor OCT or VF quality. The average RNFL thickness in the OCT scans, as well as

the MD and VFI of each VF of all eligible visits were collected.

The glaucoma stage for each eye was based on the criteria by Hodapp-Parrish-Anderson[20] (i.e., normal, mild, moderate, and advanced glaucoma). To expand our investigations, advanced glaucoma was further divided into two stages; an advanced stage, defined as an MD between $\leq-12$ and $>-18$ dB, and a severe stage, defined as an MD $\leq-18$ dB.

## CNR Calculation

The CNR is related to the signal-to-noise-ratio (*SNR*), which is defined as:

$$SNR = \frac{\mu}{\sigma},$$

where the signal ($\mu$) is divided by the variability ($\sigma$) of a measurement. The ratio represents the magnitude of signal related to the magnitude of noise of a measurement. A higher ratio represents a larger signal (i.e., power or strength of the measurement) compared to the noise. The higher the ratio, the more sensitive is the measurement at detecting the desired strength of the signal. As we were interested in assessing the sensitivity of a measurement for detecting progression or the transition between two successive stages, the signal was, therefore, represented by the contrast, which was defined as the change in the parameter between two successive stages ($\mu_a - \mu_b$). The noise was defined as the variability of the parameter in those stages ($\sigma_{ab}$).

When analyzing the variability of a measurement with multiple tests, change or disease progression in the time between these tests might still have occurred. This possible change can be accounted for by using regression on longitudinal data and subsequently the reproducibility may be determined from a residual analysis. This approach, described by Russell et al.,[21] also accounts for the factors that may change the variability over time (e.g., patient fatigue or the severity of the disease) and, therefore, provides a more accurate estimation of the measurements variability for our method ($\sigma_{ab}$). To assess the variability of each parameter for two successive stages ($\sigma_{ab}$), we performed an analysis of residuals from linear regression of the data from five subsequent visits per eye (Fig. 1). The glaucoma stage for each eye then was determined by the value of the MD on the regression line halfway between the first and fifth visits. Under the assumption that progression occurs at a fixed rate, the residuals from these analyses represent the variability over time of the parameter

for that eye.[21] For each eye $i$, the noise $\sigma_i$ was based on the residual sum of squares (RSS) of the regression analysis and was calculated by:

$$\sigma_i = \sqrt{\frac{\text{RSS}_i}{n-2}},$$

where $n$ is the number of visits per eye ($n = 5$). Here, the number of degrees of freedom is $n - 2$, because two degrees of freedom are lost due to estimation of the mean and regression slope.

The average noise for each glaucoma stage was calculated by:

$$\sigma_A = \sqrt{\frac{\sum_{i \in A} RSS_i}{n_A(n-2)}} \quad \text{and}$$

$$\sigma_B = \sqrt{\frac{\sum_{i \in B} RSS_i}{n_B(n-2)}},$$

where $\sigma_A$ is the mean noise in stage A, $n_A$ is the number of eyes in this stage, $\sigma_B$ is the mean noise of the subsequent stage and $n_B$ the number of eyes in that stage. The noise ($\sigma_{AB}$) for the transition between two successive stages (e.g., mild to moderate glaucoma) then was calculated as the average noise for these two stages by:

$$\sigma_{AB} = \sqrt{\frac{\sigma_A{}^2 + \sigma_B{}^2}{2}}.$$

The contrast was calculated by the difference in the means from each stage, $\mu_A - \mu_B$, where $\mu_A$ is the mean of the parameter in one stage and $\mu_B$ is the mean of the parameter in the subsequent stage. Thus, the contrast represents the effective measuring range of the measurement for detecting progression (i.e., the average measured difference between two successive stages). For example, the contrast for the VFI for the transition from normal to mild glaucoma is calculated as the difference between the mean VFI from all normal eyes and the mean VFI from all mildly glaucomatous eyes.

Finally, the contrast to noise ratio ($CNR_{AB}$) was calculated by:

$$CNR_{AB} = \frac{\mu_A - \mu_B}{\sigma_{AB}}.$$

The MD and VFI are corrected for age by design. The average RNFL thickness, however, is not. The median rate of RNFL thinning in our normal group was $-0.14$ μm/y, which is consistent with earlier reported thinning rates.[22,23] In case of any age
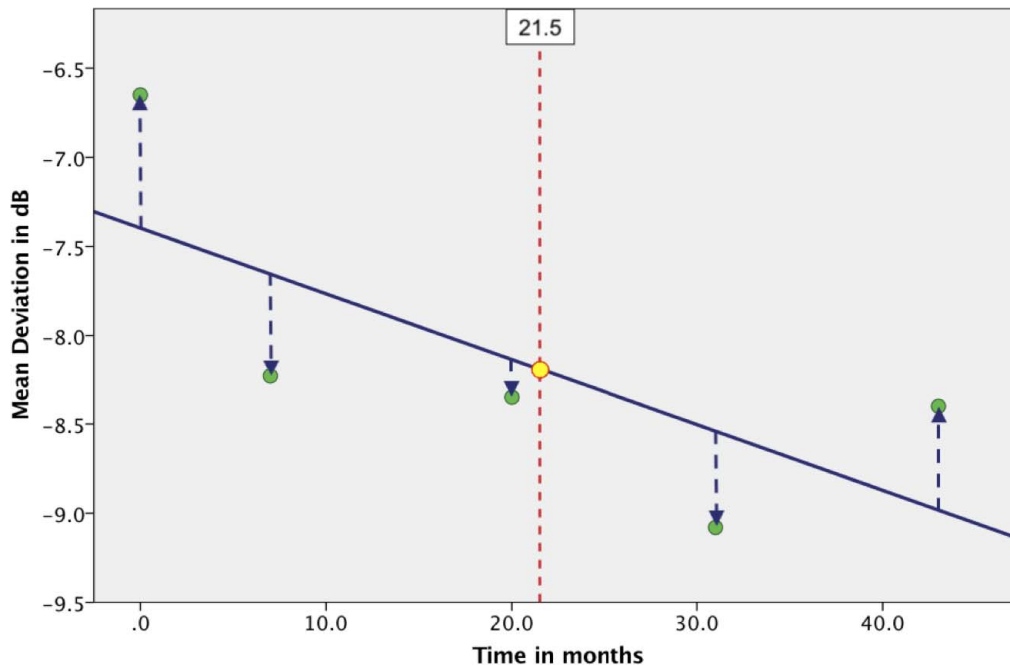
**Figure 1.** An example of a linear regression model with the MD from standard automated perimetry against time. The *green dots* represent the MD measurements of each visit in a follow-up period of 43 months from a glaucomatous eye with an estimated progression rate of −0.48 dB/year. The *dashed blue lines* represent the residual errors that indicate the difference between the observed value (*green dot*) and the value from the regression model (*blue line*). The stage of this eye was determined by the MD value on the regression line halfway between the first and fifth visits. The MD at this point was −8.19 (*yellow dot*) and so this eye was staged as moderate glaucoma.

differences between the groups, the RNFL thickness data for these groups was adjusted for this aging effect.

## Statistics

Data were collected from the case report forms of the GIS and analyzed with IBM SPSS Statistics Software (version 24; SPSS, Inc., Chicago, IL). Mean and standard deviations of the characteristics and study parameters per (sub)group were evaluated. Nonparametric tests (Mann-Whitney $U$ and Kruskal Wallis $H$ for continuous variables and binomial tests and $\chi^2$ for categorical variables) were used for statistical analysis. For comparison of the noise between the different stages, the Kruskal Wallis test was used. $P < 0.05$ was considered statistically significant.

For comparison of the CNRs between transitions and between parameters, a bootstrap sampling technique was used to determine 95% confidence intervals (CIs) for the difference of the CNR across stages and between parameters (MD, VFI, and RNFL). Values outside the 95% CI were considered a statistically significant difference. The statistical

software R (version 3.4.3, 2017-11-30) was used for the bootstrap analysis.

## Results

We included 205 eyes from 125 participants (54% women; 46% men) for the analysis. There were 82 eyes in the normal group and 123 in the glaucoma group. Of all 123 glaucomatous eyes, 36 had mild, 32 moderate, 38 advanced, and 17 severe glaucoma. Characteristics of the normal and glaucoma groups and for each of the glaucoma subgroups separately are shown in Tables 1 and 2, respectively. The normal group was significantly younger (median, 58 years; interquartile ratio [IQR], 47–67) compared to the glaucoma group (median, 68 years; IQR, 61–75) and the time between the first and fifth included visits was significantly longer in the normal group (median, 70 months; IQR, 62–78) compared to the glaucoma group (median, 48 months; IQR, 42–54). Post hoc Dunn-Bonferroni correction showed a significant difference for age between the normal and mild, normal and moderate, and normal and advanced subgroups ($P < 0.05$). The time variable only differed

**Table 1.** Descriptive Statistics

|  | Normal, $n = 82$ | Glaucoma, $n = 123$ | P Value |
|---|---|---|---|
| Female sex, % | 57 | 51 | 0.39[a] |
|  | Median (IQR) | Median (IQR) |  |
| Age, y | 58 (47–67) | 68 (61–75) | <0.0001[c] |
| Time, months | 70 (62–78) | 48 (42–54) | <0.0001[c] |
| RNFL, μm | 93 (87–99)[b] | 57 (49–64) | <0.0001[c] |
| MD, dB | 0.1 (−0.6 to 0.8) | −9.8 (−15.5 to −0.9) | <0.0001[c] |
| VFI, % | 99 (99–100) | 74 (54–89) | <0.0001[c] |

Time, time in months between the first and fifth visits.
[a] $\chi^2$ test.
[b] Not age corrected.
[c] Mann-Whitney $U$ test.

significantly between the normal and mild subgroups ($P < 0.05$). There were no significant differences for age and time variables between the remaining successive stages. The average RNFL thickness, MD, and VFI were significantly different between the normal and glaucoma groups and between successive stages. Post hoc Dunn-Bonferroni correction showed significant differences for the study parameters (RNFL, MD, and VFI) between all successive stages ($P < 0.05$), except for the average RNFL thickness between the moderate and advanced subgroups ($P = 1.00$).

## Noise and Contrast Results

Mean age difference between the normal and glaucoma groups was 8 years. Therefore, −1.1 μm (8 ∗ −0.14 μm) was added to the estimation of the average RNFL thickness for the normal group to correct for age in the calculation of the contrast for

the transition from normal to mild glaucoma. No significant differences in age between the remaining successive stages was found. Therefore, the RNFL thickness for these stages was not corrected for age.

The noise per eye has been presented for the various parameters in Figure 2. The locally weighted RNFL noise was relatively constant within the spectrum of healthy to severe glaucomatous eyes <2.1 μm. The locally weighted MD noise increased at the onset of glaucoma and then declined again beyond an average MD value of −12 dB. The locally weighted VFI noise showed a similar trend as the MD, though with a steeper course at the beginning. Descriptive statistics of the noise per eye for the various subgroups are shown in Table 3.

The mean contrast and noise values for the transitions between the various stages of the disease and for each parameter separately are presented in Figure 3. The contrast of the mean RNFL thickness

**Table 2.** Descriptive Statistics

|  | Normal, $n = 82$ | Mild, $n = 36$ | Moderate, $n = 32$ | Advanced, $n = 38$ | Severe, $n = 17$ | P Value |
|---|---|---|---|---|---|---|
| Female sex, % | 57 | 56 | 44 | 47 | 65 | 0.53[a] |
|  | Median (IQR) | Median (IQR) | (IQR) | Median (IQR) | Median (IQR) |  |
| Age, y | 58 (47–67) | 67 (63–75) | 70 (62–75) | 68 (61–74) | 68 (54–75) | <0.0001[c] |
| Time, m | 72 (62–78) | 43 (41–48) | 48 (43–63) | 46 (42–55) | 48 (44–49) | <0.0001[c] |
| RNFL, μm | 93 (87–99)[b] | 64 (59–71) | 58 (49–62) | 54 (49–61) | 45 (41–52) | <0.0001[c] |
| MD, dB | 0.1 (−0.6 to 0.8) | −3.5 (−4.8 to −2.2) | −7.5 (−9.6 to −6.0) | −14.2 (16.5 to −12.9) | −21.4 (−24.7 to −19.6) | <0.0001[c] |
| VFI, % | 99 (99–100) | 92 (88–94) | 81 (75–87) | 59 (52–5) | 35 (29–44) | <0.0001[c] |

Time, time in months between the first and fifth visit.
[a] $\chi^2$ test.
[b] Not age corrected.
[c] Kruskal-Wallis $H$ test.
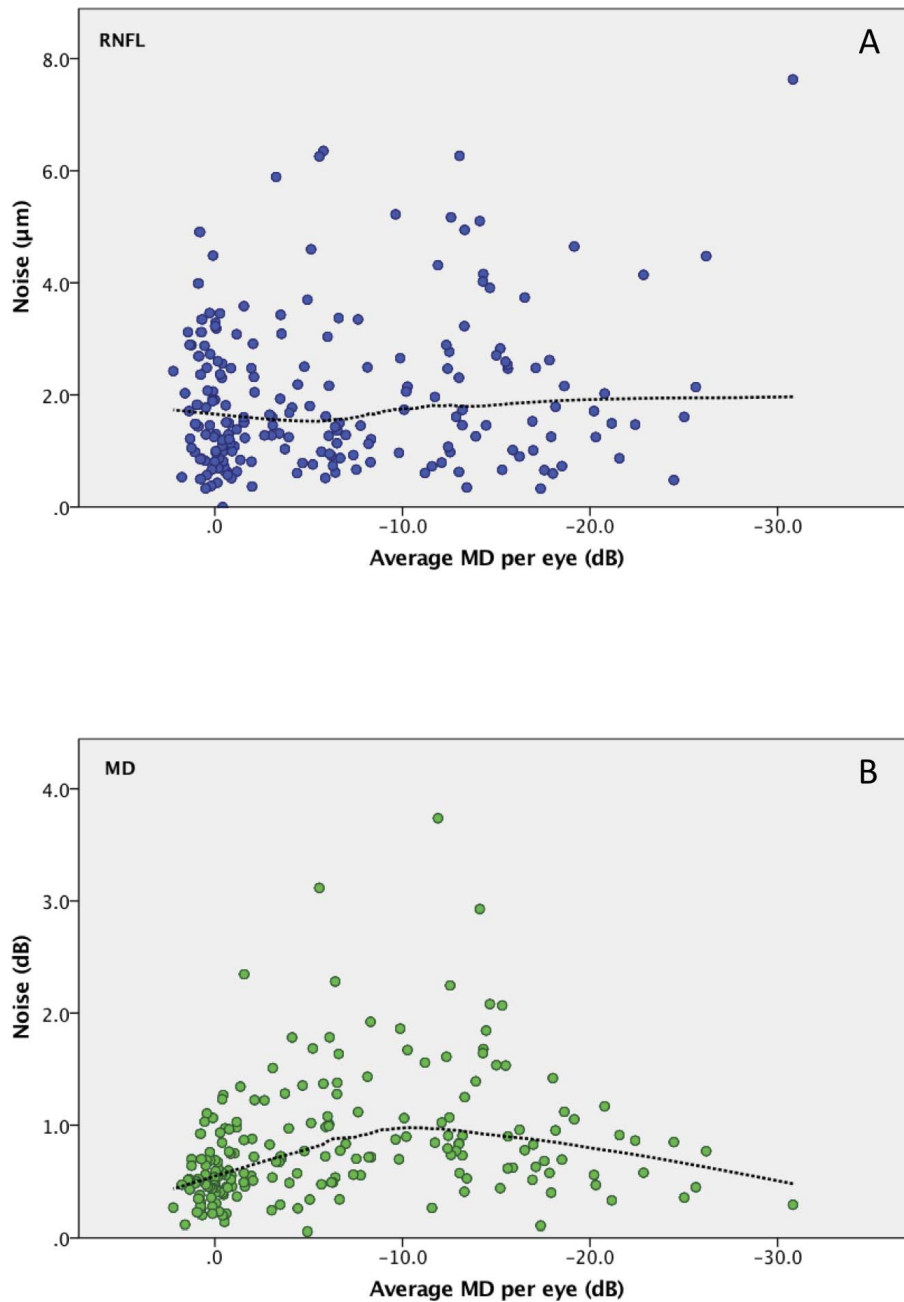
**Figure 2.** Scatterplot of the noise (*y*-axes) of each eye (*colored dots*) for the RNFL thickness (A), MD (B) and VFI (C). The value along the *x*-axes of each dot corresponds to the average MD value of the eye. The *dashed black line* is the locally weighted regression line of the scatterplot (LOWESS fit with 95% CI, 75% of points to fit, Epanechnikov kernel).

shows a decrease as glaucoma progresses. The contrast of the MD and VFI, however, increased with more advanced glaucoma.

## CNR Results

The CNR calculations for each parameter and for the various transitions are shown in Figure 4. The CNR for the RNFL thickness was highest in the transition from normal to mild glaucomatous eyes and differed statistically significantly from the CNR for the transition from mild to moderate glaucomatous eyes (CNR RNFL 12.2 vs. 3.3; 95% CI, 5.7–12.2). There were no significant differences between the last three transitions (CNR range, 0.8–3.3), indicating that the RNFL thickness is most sensitive
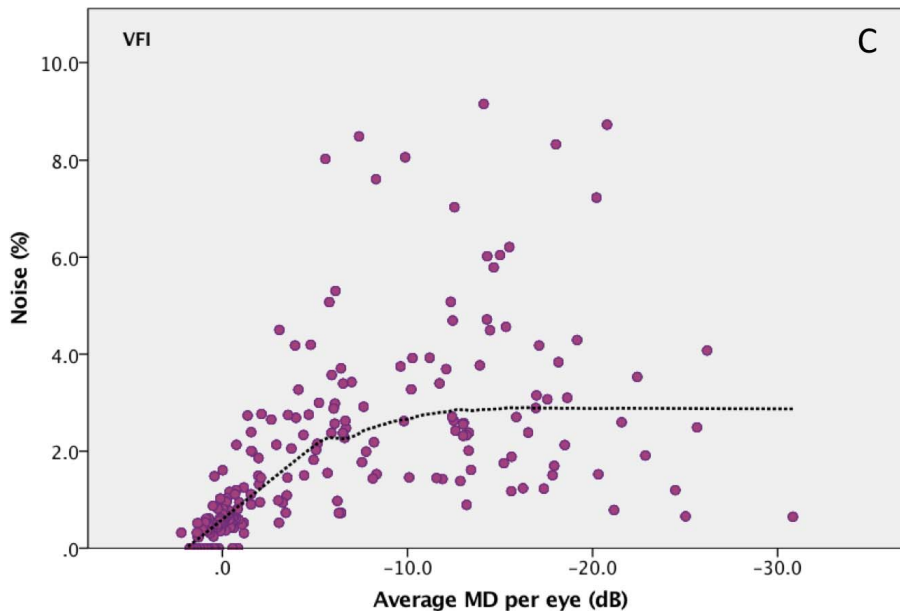
**Figure 2.** Continued.

at detecting progression from normal to mild glaucoma. The CNR of the MD and VFI were largest in the last two transitions (CNR MD 5.2 and 7.2, CNR VFI 5.8 and 5.8). We found a statistically significant difference for the CNR of the MD and of the VFI between the transition from mild to moderate and moderate to advanced glaucoma (CNR MD 3.6 vs. 5.2; 95% CI, [−3.1,−0.1], CNR VFI 3.2 vs. 5.8; 95% CI, [−4.4,−0.8]). No statistically significant differences were found for the CNRs of the MD and VFI between the other successive transitions, indicating that the MD and VFI are most sensitive for detecting progression from moderate to advanced and advanced to severe glaucoma.

The RNFL thickness had a higher CNR in the transition from normal to mild glaucoma compared to the MD and VFI and differed statistically significantly (CNR MD 4.1 vs. CNR RNFL 12.2, 95% CI [−10.8,−5.7]; CNR VFI 4.5 vs. CNR RNFL 12.2; 95% CI, [−10.1,−5.5]), indicating that the RNFL thickness is more sensitive for detecting progression at the onset of glaucoma compared to the functional measures. The functional measures showed higher CNRs compared to the RNFL thickness in the transition from moderate to advanced and advanced to severe glaucoma, and MD and VFI differed statistically significantly from the RNFL thickness in both transitions (CNR MD 5.2 vs. CNR RNFL 0.8, and CNR MD 7.2 vs. CNR RNFL 3.2; 95% CI, [2.7,5.9], [1.7,6.5], CNR VFI 5.8 vs. CNR RNFL 0.8, and CNR VFI 5.8 vs. CNR RNFL 3.2; 95% CI, [3.2,6.7], [0.2,5.3], respectively) indicating that the functional measures are more sensitive for detecting progression in later stages of glaucoma compared to the RNFL thickness. No statistically significant differences were found between the CNRs of the structural and functional measures in the transition from mild to moderate glaucoma and between the CNR of the MD and VFI in all four transitions.

**Table 3.** Mean (and Standard Deviation) of Noise per Eye for the Various Stages

|  | Normal, $n = 82$ | Mild, $n = 36$ | Moderate, $n = 32$ | Advanced, $n = 38$ | Severe, $n = 17$ | P Value |
|---|---|---|---|---|---|---|
| RNFL, um | 1.8 (1.1) | 2.1 (1.5) | 1.7 (1.1) | 2.3 (1.5) | 2.3 (1.8) | <0.0001 |
| MD, dB | 0.6 (0.3) | 0.9 (0.6) | 1.1 (0.7) | 1.1 (0.6) | 0.8 (0.3) | <0.0001 |
| VFI, % | 0.6 (0.5) | 2.4 (1.5) | 3.1 (1.9) | 3.3 (1.9) | 3.4 (2.5) | <0.0001 |

Kruskal-Wallis H test. Post hoc Dunn-Bonferroni showed only a significant difference for the average RNFL thickness and MD noise per eye between the moderate and advanced glaucoma subgroup and for the VFI noise per eye between the normal and mild glaucoma subgroup and ($P < 0.05$).
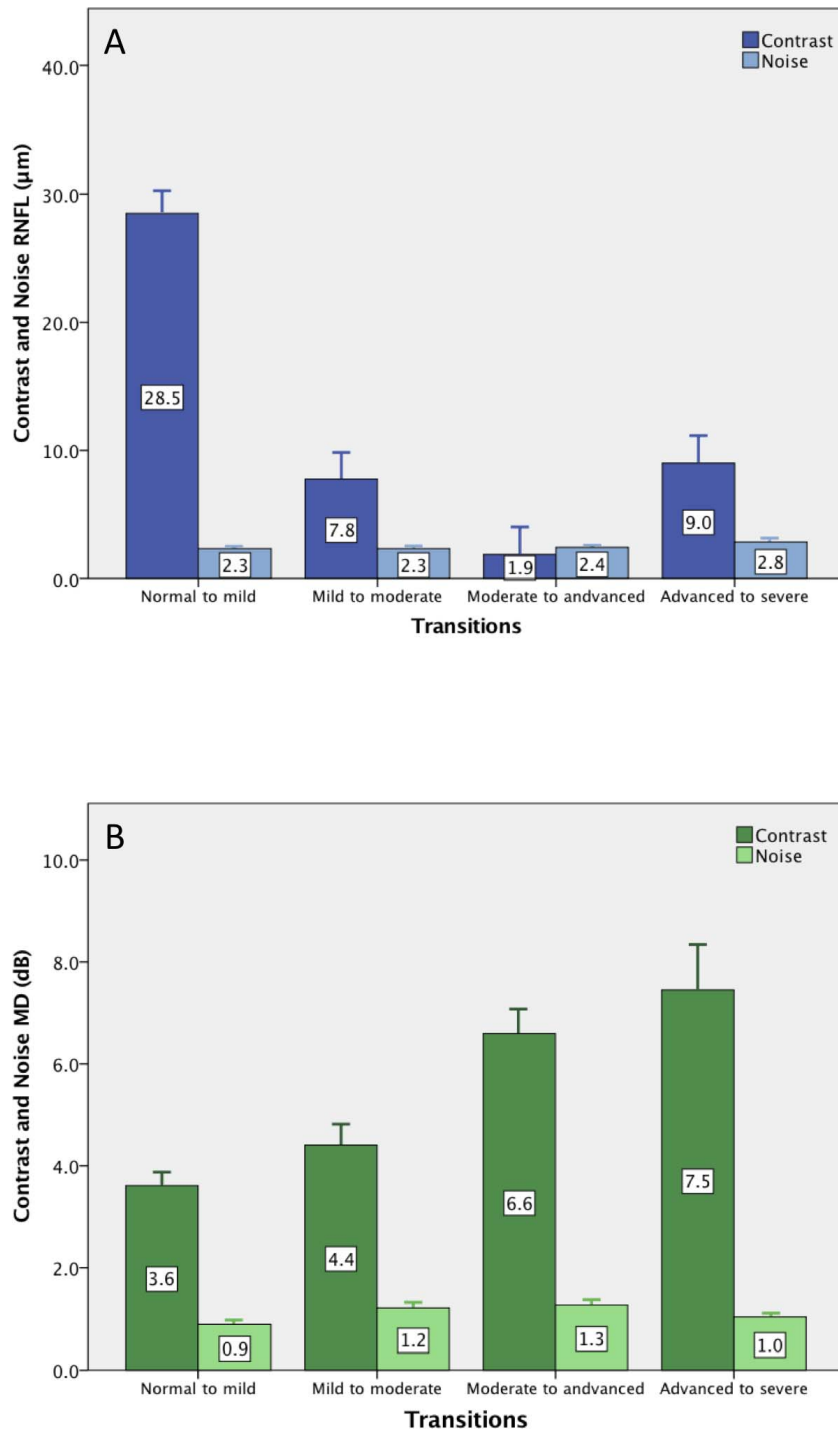
**Figure 3.** Mean contrast and noise values. *Box plot* of the mean contrast and noise for the RNFL thickness (A), MD (B), and VFI (C). The *whiskers* indicate the standard error of the mean.

## Discussion

By using CNRs, we have, for the first time to our knowledge, determined how sensitive OCT and SAP are for detecting glaucomatous progression. We showed that the RNFL thickness from OCT is most sensitive for detecting progression at the onset of glaucoma compared to the functional measures from SAP, while the latter are more sensitive for detecting
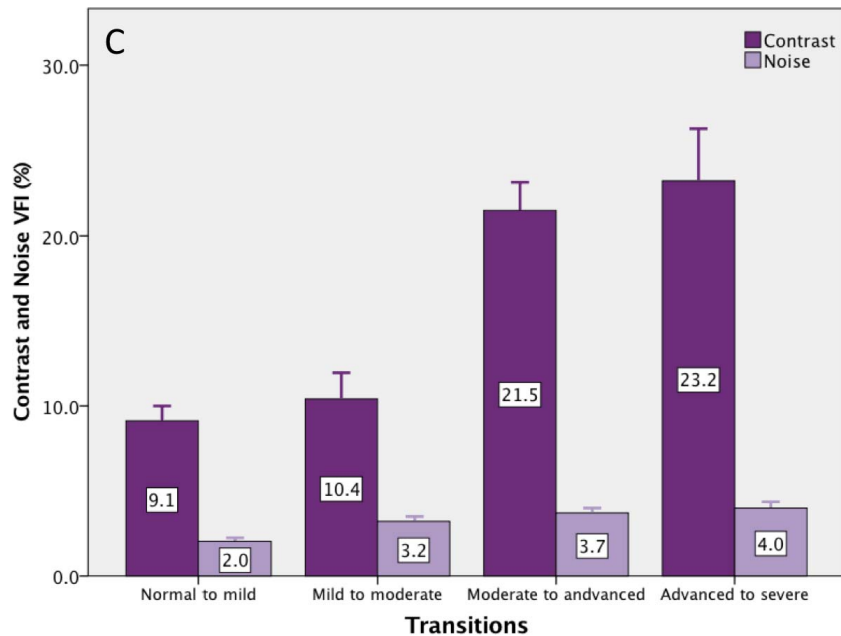
**Figure 3.** Continued.

progression in the later stages of glaucoma. The MD and VFI demonstrated similar sensitivities for the detection of progression across the disease spectrum. These findings are consistent with prior literature suggesting that structural tests are better used in early stages of glaucoma for the detection of progression, whereas functional measurements are better used in more advanced stages.[10,14–18]

This new method contains three main aspects: (1) CNRs were used to determine the ability of a measurement to detect progression between stages of glaucoma; CNR was defined as the ratio of the measured difference and the variability. (2) The clinically more relevant long-term variability was estimated from an existing pool of longitudinal data. (3) The ratio is dimensionless, allowing a direct comparison between the different types of measurements (structural and functional) for their sensitivity to detect progression.

In clinical practice, it is not clear which technology or measurement (structural or functional) is superior in detecting glaucomatous progression. Often both technologies (OCT and SAP) are used to assess progression. However, with limited resources, such an extensive approach is perhaps impossible or undesirable.[24] If we look at the summed CNR of all transitions for each technology separately, it shows that OCT and SAP are approximately equally sensitive for monitoring progression across the entire disease spectrum: their CNRs are all approximately

20. However, the structural measure is more sensitive in detecting progression earlier on in the disease, suggesting that using OCT in early stages and SAP in later stages is more cost effective. By using different instruments for monitoring different disease stages, 29 steps compared to the aforementioned 20 steps from healthy to severe glaucoma can be discriminated and one can limit the use of these technologies to only one at a time. Such a tailored and combined approach not only saves time and expenses, it also reduces the burden of testing to our patients. Combining measurements has also been supported by the work of Medeiros et al.[15] who developed a combined structure and function approach that later was used by Zhang et al.[25] to measure rates of progression in glaucoma. This approach describes a single index for estimating the number of ganglion cells in individual eyes by combining two models developed by Harwerth et al.[26]: the perimetric model, which converts SAP data into an estimate of number of ganglion cells, and the RNFL model, which converts RNFL data in a number of ganglion cells. The two models are combined in a weighted sum that relies more on the RNFL estimate at the onset of glaucoma and on the SAP estimate in the later stages of glaucoma.[15] Similar to their approach, we also took the differences between the added value of OCT and SAP for the various stages of glaucoma into account and showed that OCT is of more value for detecting progression at
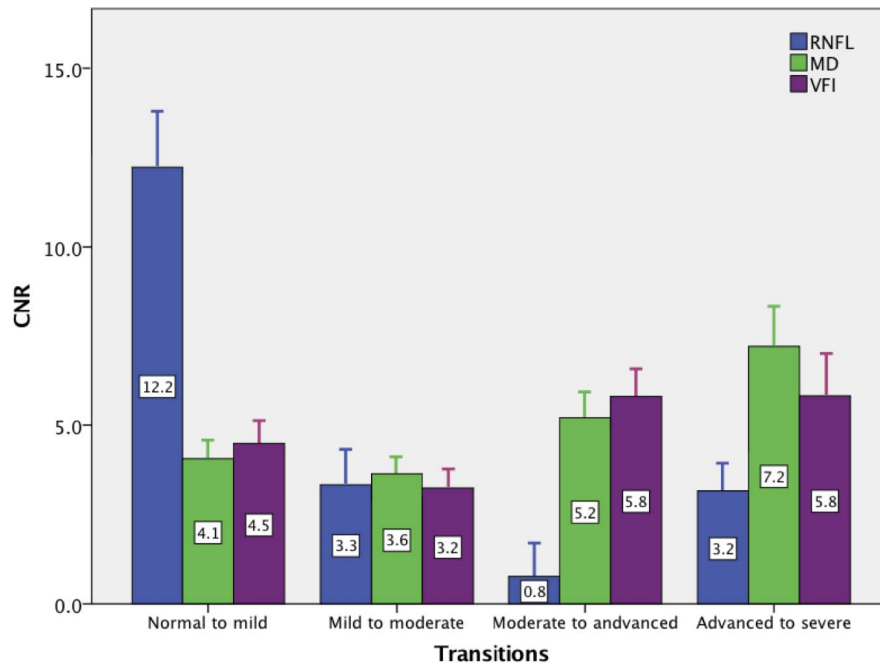
**Figure 4.** CNRs of the various parameters for the transitions between the various stages of the disease.

the onset of glaucoma and SAP is of more value for detecting progression in the later stages of glaucoma.

Gardiner et al. [23] used longitudinal SNRs (LSNRs), which were defined for each eye as the ratio of the mean annual rate of change (signal) to the standard deviation of residuals (noise) from linear regression analysis. The authors showed better mean LSNRs for the average RNFL thickness from peripapillary scans (−0.601 y-1) compared to the MD from SAP (−0.045 y-1) in 226 eyes with MDs at baseline ranging from −15.46 to 2.50 dB. The mean LSNR of a subgroup of suspected glaucomatous eyes with an MD within normal limits at baseline also showed better results for the average RNFL thickness compared to the MD. This is consistent with our results, indicating that the OCT is more sensitive for detecting progression compared to SAP at the onset of glaucoma. In their study, progression was defined as the rate of change per year. Therefore, this method could be used to determine which parameter is more sensitive for detecting progression in the short run. Contrary to our study, they did not extend their study to more advanced glaucoma.

The average RNFL thickness showed a strong decrease in the CNR in the transition from mild to moderate glaucoma. A possible explanation for this finding is the limited thinning of the RNFL at these stages of the disease. The lower limit of RNFL thickness has been estimated at approximately 38 μm, which usually occurs in the moderate and advanced stages of glaucoma.[27,28] Further RNFL thinning, therefore, is not expected at these stages and consequently the expected contrast becomes negligible.

The variability of the MD decreased at an average MD of −12 dB, leading to a decrease in the variability in the transition from advanced to severe glaucoma. It has been reported previously that a decrease in the variability of the MD can be expected in more advanced and severe cases because of the limit of the stimulus intensity at 0 dB.[21,29,30] Due to this left censoring effect, sensitivity threshold values below 0 dB, although physiologically possible, cannot be detected by the device. We also noted a decreased variability of the VFI at an average MD of −12 dB. This can be explained by the fact that the VFI of the eyes in these advanced stages approaches its "floor" of 0%. In summary, the left censoring effect of the MD and the floor effect of the VFI lead to smaller ranges in MD and VFI in the advanced and severe cases of glaucoma. This resulted in an apparent decrease in variability and consequently caused an apparent increase in the CNR for the MD and VFI in these later stages.

In this study, the glaucoma stage of each eye was based on the MD, which also was one of the

parameters in the evaluation and, therefore, may raise the question of selection bias. Indeed, when stratifying eyes by MD, the range of the other measurements (VFI and average RNFL thickness) within each group is larger than when those measurements would have been used to define the disease stages. Therefore, the same VFI or RNFL thickness can be observed in successive disease stages. This should, however, not have a considerable impact on the calculated CNRs: contrasts were based on the averages in each disease stage that were obviously not affected by symmetrical broadening of the distribution of a parameter. The noise was based on a regression model applied to individual eyes, and the resulting variability did not differ a lot between successive stages.

This study looked at the ability of global indices to detect progression from one stage to the next. For future work, it would be interesting also to look at CNR differences between parts of the VF or areas within the OCT map. If there is a difference in glaucoma severity between damaged and healthy parts within one eye, there also are differences in contrast and noise between these local parts. Therefore, the CNR of the summary parameters may underestimate the CNR at a local level in some areas, while overestimating it in other regions. It may be feasible to locally monitor the better parts within one eye by OCT and the damaged parts by SAP. Investigating the CNR locally could help in determining the best technology for monitoring glaucoma progression on a more patient-specific level. In addition, other measurements that are used in the clinic for the detection and monitoring of glaucoma must be evaluated. For example, thinning of the ganglion cell complex (GCC) in the macula occurs in glaucoma and can be detected with OCT macular scans.[31,32] However, this damaged area often passes unnoticed in the RNFL thickness with OCT peripapillary circle scans.[33] Furthermore, it has been suggested that the thickness of the GCC is better for detecting progression in the more advanced stages of glaucoma than the RNFL thickness.[18,27]

In conclusion, we showed that the CNR method can be used to assess which parameter and which measurement technique is most sensitive for detecting glaucomatous progression, differentiated for the severity of the disease. Furthermore, this method is not limited to the management of glaucoma but might prove helpful in evaluating the sensitivity of progression detection in other diseases or eye diseases as well.

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