

Correlation of visual changes with disc morphology

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Abstract

The identification of glaucomatous damage and monitoring of disease progression require the measurement of both structural and functional changes. Ongoing research is focused on the relationship between these two types of changes. The purpose of this paper is to examine four aspects of the association between structural and functional changes of the optic nerve head (ONH)—the spatial relationship between changes in the ONH and visual field, the quantitative relationship between these changes, the difficulties of using summary statistics to quantify damage, and a comparison of how structure and function measurements allow us to detect progression and how these measurements agree with each other. Dissociation between structural and functional measurements may occur—it is possible that some structural change does not relate to ganglion cell loss, and some functional loss does not relate to cell loss but to dysfunction. Current data suggest that both structural and functional measurements are necessary to monitor disease progression, which is important for making clinical decisions.

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Introduction

The identification of glaucomatous damage and monitoring of disease progression require the measurement of both structural and functional changes. Ongoing research is focused on the relationship between these two types of changes. The purpose of this paper is to examine four aspects of the correlation between structural and functional changes of the optic nerve head (ONH)—the spatial relationship

between changes in the ONH and visual field (VF), the quantitative relationship between these changes, the difficulties of using summary statistics to quantify damage, and a comparison of how structure and function measurements allow us to detect progression and how these measurements agree with each other.

Spatial relationship between changes in the nerve and the visual field

In 2000, we examined the relationship between the VF test points in the Humphrey 24-2 test pattern and sectors of the ONH.¹ The VF grid was appropriately scaled and overlaid onto retinal nerve fibre layer photographs. We centred the VF on the fovea, with a circle marking the ONH, and then followed the margins of defects or prominent nerve fibre bundles to see where individual VF test points would be related at the ONH. A clinically useful map was produced, which relates VF field test points to regions of the ONH (Figure 1). This map, however, provides only an anatomical description, and does not relate function to structure.

Gardiner *et al*² produced a different type of map, a topographical map of the relationship between sectors of the ONH and locations in the VF (Figure 2). Specifically, they looked at the correlation between Heidelberg retina tomograph (HRT) neuroretinal rim area (NRA) and VF sensitivity at each point in the VF. For most points in the VF, there was a fairly good correspondence between the actual structure/function correlations in glaucoma patients and those from the anatomical map (Figure 1). However, there were exceptions where correspondence was less good, particularly in the more peripheral VF and in the temporal VF. It is difficult to be certain why those exceptions occurred, but the possibilities include a limited range of sensitivity values, which would make correlations less strong, the fact

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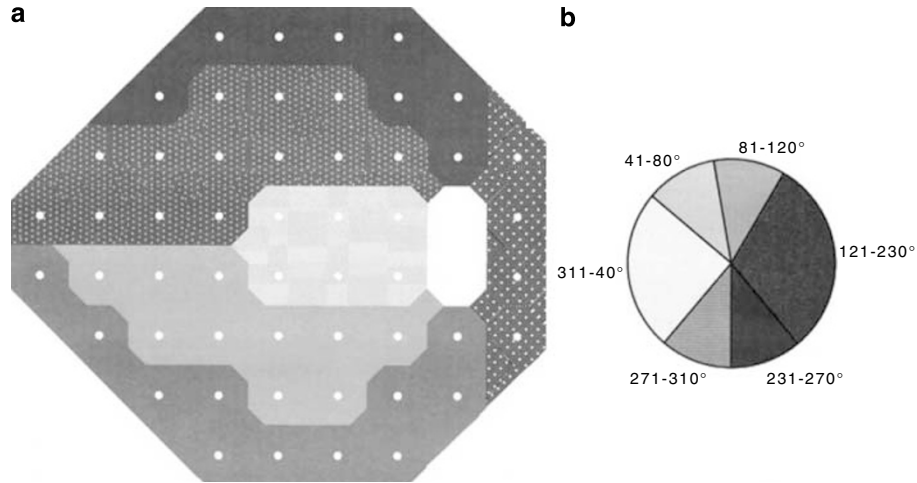


Figure 1 A division of the visual field (a) and optic nerve head (b) into mapped sectors according to the results of a study of defects in 69 normal-tension glaucoma or glaucoma suspect patients. (Reproduced from Garway-Heath *et al*¹ with permission of *Ophthalmology*, Copyright 2000, with permission from Elsevier.)

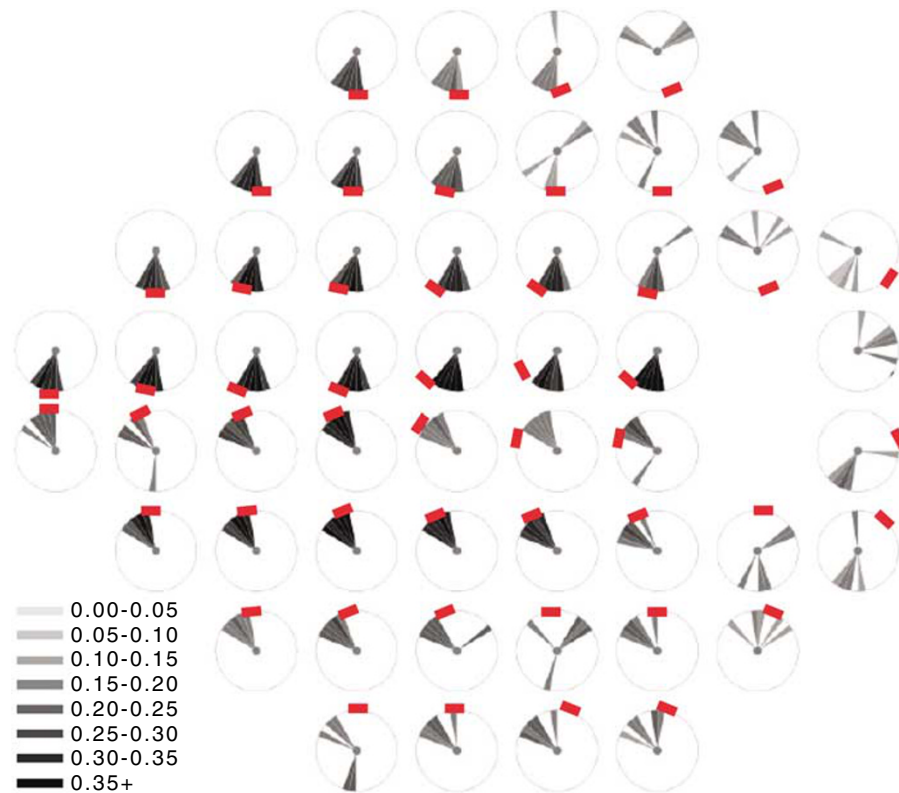


Figure 2 Topographical map of the relationship between sectors of the ONH and locations in the visual field, using empirical cross-sectional patient data; the shade of grey in the sectors indicates the strength of correlation. The red bar indicates the location of expected strongest correlation on the basis of the map given in Figure 1. (Reproduced from Gardiner *et al*² with permission of *Invest Ophthalmol Vis Sci* via Copyright Clearance Center.) ONH, optic nerve head.

that the HRT-NRA values include blood vessels (which confounds the true NRA measurement more in some parts of the ONH than others), the greater inter-individual variability of NRA in some sectors and of

some VF test points, and the fact that VF test points (and NRA sectors) are not independent of each other. Nevertheless, at least some functional/structural correlation is possible.

Quantitative relationship

In a 1985 paper by Airaksinen *et al.*,³ magnification-corrected measurements of the NRA were found to be highly significantly associated with VF sensitivity in a nonlinear manner. A similar nonlinear association was found in a study by Bartz-Schmidt *et al.*,⁴ in which the NRA was measured with the HRT.

A study was conducted in 1999 to investigate the relationship between electrophysiological, psychophysical, and anatomical measurements in glaucoma.⁵ The parameters measured were VF sensitivity, the pattern electroretinogram amplitude (believed to reflect function in the inner retina⁶), and the NRA in the temporal half of the ONH using the HRT. The association between variables was investigated by linear and quadratic regression analysis. The quadratic (nonlinear) regression fits were stronger than the linear. The findings of a nonlinear fit suggest that, at all stages of disease, loss of ganglion cells is associated with a loss of function, albeit with a changing structure/function slope at different stages of disease (a shallow structure/function slope in early disease and a steep structure/function slope in later disease). This supports the hypothesis that there is no RGC reserve that has to be lost before functional deficits manifest but, instead, there is a continuous structure/function relationship and any loss in RGCs will manifest in reduced VF sensitivity. The pattern of the structure/function association suggested by this research is that, in early disease, VF changes, scaled in dB loss, occur relatively slowly compared with structural changes. Later in the disease, functional changes are more marked than structural changes. It may be that, if the VF were tested and quantified on a linear (rather than dB) scale,⁷ functional and structural measures may have a more linear association and change similarly, regardless of stage of disease.

Summary statistics

There is some difficulty in using summary statistics to relate structure and function arising from differences in the way in which RGCs are quantified. If the ONH is divided into equal sectors, and the sectors are related to the VF map (Figure 1), there is considerable variation in the number of VF test points examined in each ONH sector. In some 30° sectors, there may be nine test points (such as an infero-temporal ONH sector), whereas in others there may only be two, or none. Therefore, an average of VF test point sensitivity will be weighted towards certain parts of the ONH. Another problem is the relationship between density of VF test points and RGC density. The VF has a regular grid of test points, whereas RGC density is much greater near the fovea than

peripherally. If mean deviation is used as a summary statistic, there is disproportionate weighting in favour of the peripheral field compared with the central field. The implication is that estimates of disease severity and progression rate may differ between investigations (structural and functional), because of differences in sampling of the VF and in scaling.

Detection of progression

There is conflicting evidence as to how imaging compares with VF testing in detecting progression. In the Ocular Hypertension Treatment Study,⁸ a large proportion of patients whose disease progressed were picked up by imaging, whereas virtually none was identified in the Early Manifest Glaucoma Trial.⁹ However, it is difficult to compare the two studies, because of differences in methodology and criteria applied, and a lack of external validation of change criteria.

A study that specifically compared estimates of progression from series of HRT images and VF tests found that a much greater number of patients with established glaucomatous VF loss were identified as progressing from the HRT images series.¹⁰ Again, the results are criterion-dependent and without an estimate of specificity for the chosen criteria. It is difficult to determine, therefore, whether the HRT and VF change criteria were located at a different part of a similar receiver operating characteristic (ROC) curve (with differing levels of specificity) or were located at similar parts of a differently shaped ROC curve (with similar levels of specificity) (Figure 3).

This issue was partly addressed in a later study of the same group of glaucoma patients and normal controls, who were followed up prospectively for 7 years for evidence of the relationship between VF and ONH changes using standard automated perimetry (SAP) and HRT.¹⁰ Three different sets of criteria were compared—most conservative, intermediate, and least conservative. The analysis was balanced so that roughly the same number of subjects would be progressing by

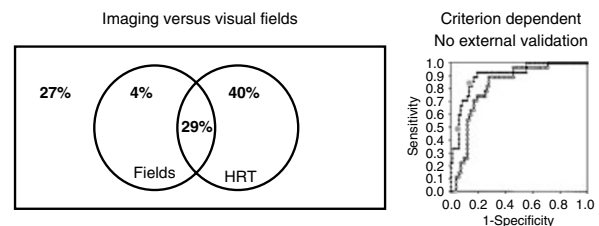


Figure 3 Poor correlation between imaging and visual fields: progression was detected by both techniques in few eyes.

structure and function criteria at each stringency level. Although SAP and HRT detected roughly equal numbers, the overlap was poor; different eyes progressed by one modality or the other, and few by both (Figure 4).

A similar study¹² considered HRT and VF data over time for 192 ocular hypertensive patients, some of whom had developed VF loss during the observation period, and for 21 normal subjects. Linear regression analysis was used to define HRT-NRA and VF progression, and change criteria were adjusted to obtain particular levels of specificity (as judged by the proportion of subjects showing significant positive change and by the proportion of normal subjects showing significant negative change). When the specificity level was set at about 90%, roughly equal numbers progressed according to HRT and VF, with a relatively small overlap between the two. Two-thirds of the patients in the overlap changed in corresponding regions of the ONH and VF.

With more stringent criteria and a specificity set at 97%, fewer cases were detected — about 9% with HRT and 15% by VF—but the very small overlap had 100% congruity between structure and function change (Figure 5).

The most likely cause for the lack of concordance between structural and functional estimates of progression in glaucoma is that ‘noise’ in the measurement system is greater for one modality than the other in some patients. It is also possible that some structural changes that occur are not directly related to RGC loss (such as lamina cribrosa bowing), or that functional loss is unrelated to RGC loss but related to RGC dysfunction, non-RGC retinal disease, cataract development or posterior visual pathway disease. Indeed, it has been suggested that reversible RGC dysfunction may be a significant component of the loss of function seen in glaucoma.¹³

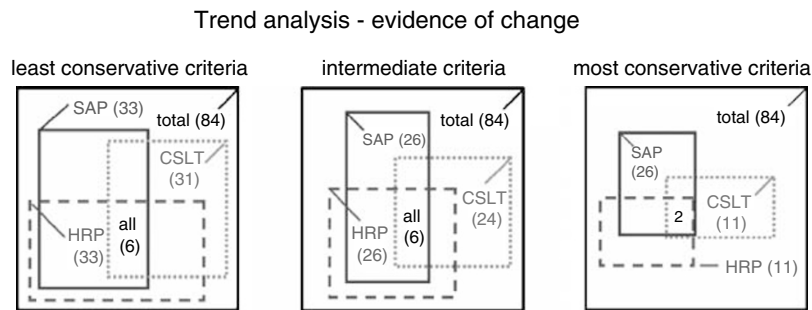


Figure 4 Venn diagram of the classifications with least conservative, intermediate and most conservative criteria, based on EOC criteria. (Reproduced from Artes and Chauhan,¹¹ with permission of *Prog Retinal Res* from Elsevier.)

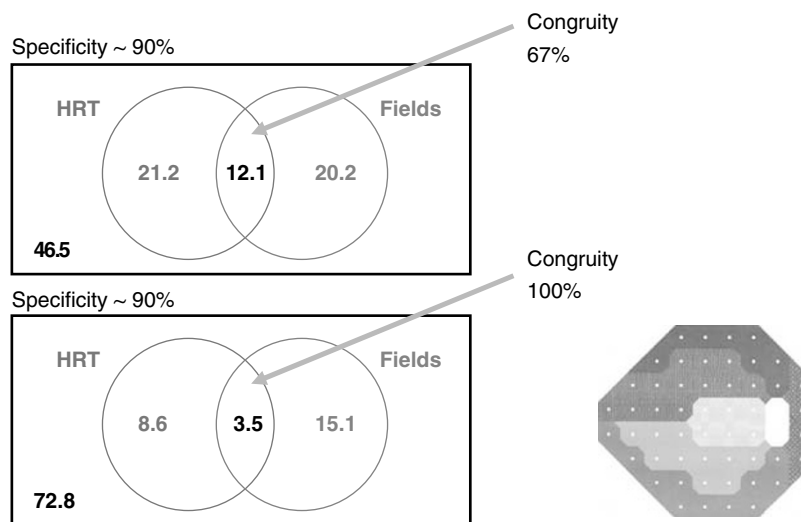


Figure 5 Specificity and congruity for HRT and visual field examination in 192 ocular hypertensive patients. (Reproduced with Strouthidis *et al*¹² with permission of *Invest Ophthalmol Vis Sci* via Copyright Clearance Center.) HRT, Heidelberg retinal tomograph. The numbers in the bottom left corners are: ‘Percentage of stable patients’. The numbers in the Venn diagrams are: ‘Percentage of patients identified as progressing by perimetry and imaging’.

Conclusion

It can be concluded from the evidence presented that the previously held belief, that structural tests are better than functional tests to identify abnormality or progression in OHT and early glaucoma, is not justified. Dissociation between structural and functional measurements may occur—it is possible that some structural change does not directly relate to RGC loss, and some functional loss does not directly relate to structural loss but to dysfunction. Current data suggest that both structural and functional measurements are necessary to monitor disease progression.

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