Clustered spatial alignment of ganglion cell structure and function delivers near perfect correlation

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Purpose

Structure-function models of the retinal ganglion cell layer are limited by spatial inconsistencies and high measurement variability. Suboptimal account of physiological changes over time delays the identification of deviations, such as early changes with glaucomatous disease. Current advances aim to develop normative structural databases and establish correlation with spatially summated functional parameters resulting in the prediction of visual field sensitivity from easily accessible ganglion cell thickness data.

Introduction

We have previously demonstrated that structural and functional changes to the optic nerve head (ONH) with age and disease are highly concordant,[1] but depend on

- Precise spatial alignment for structural and functional measurements,
- Robust automated layer segmentation to facilitate reliable estimation of ganglion cells per stimulus area through surrogate measurements, and
- Accurate modelling of clustered data signifying areas of equivalent change.

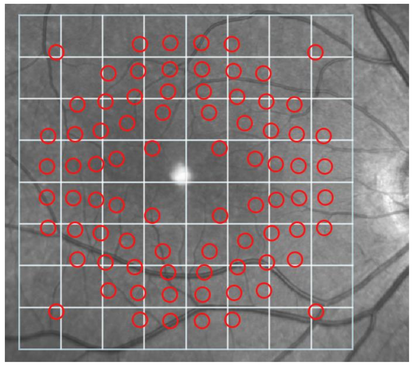

Figure 1.
Retinal thickness data, historically averaged over a semi-arbitrary 8x8 grid (white grid), have been reconciled to coincide with locations projected by visual field stimuli including adjustment for microsaccades and Drasdo correction (red circles).

Methods

- Spectralis optical coherence tomography of the central macular 30x25° field was collected from 254 patients without pathological changes to the posterior pole (**Table 1**).
- Areas spatially coinciding with projections of Goldman III stimulus sizes at 10-2 and paracentral 30-2 Humphrey visual field test locations were identified accounting for Henle fibre displacement and microsaccades.
- Average ganglion cell layer (**GCL**) and inner plexiform layer (**IPL**) thicknesses were extracted using a customised Matlab algorithm. K-means cluster analysis identified areas with similar change over time.

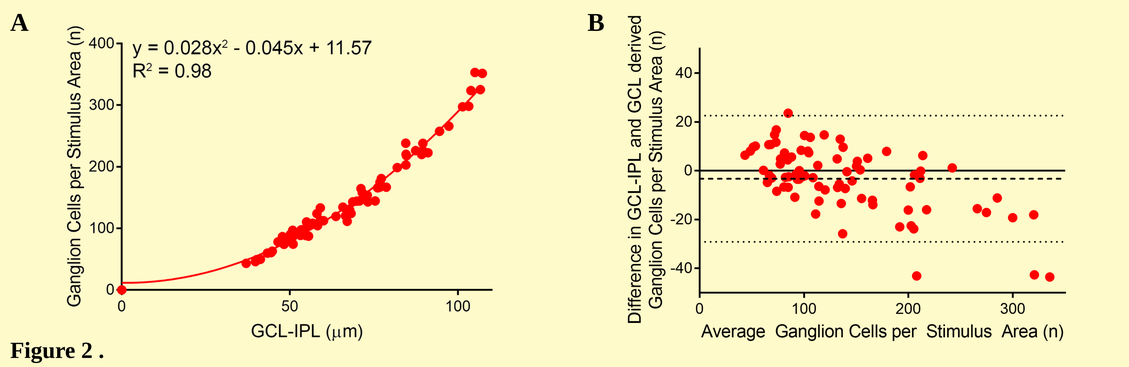

Figure 2 .
(**A**) Correlation between GCL-IPL thickness and ganglion cells per stimulus area (GCpSA) calculated from GCL thickness only for data age-corrected to the 50-year equivalent[2], which subsequently allows to calculate GCpSA from the more robust GCL-IPL measurements. (**B**) Bland-Altman plot demonstrating the accuracy of GCpSA calculated from GCL-IPL measurements (black dashed line: average bias, black dotted lines: 95% limits of agreement).

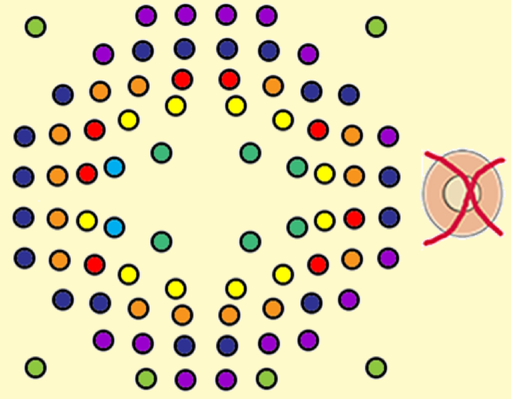

Figure 3.
GCL-IPL derived measurements formed a concentric pattern based on eight statistically separable K-means clusters consistent with areas of similar structural change over time .

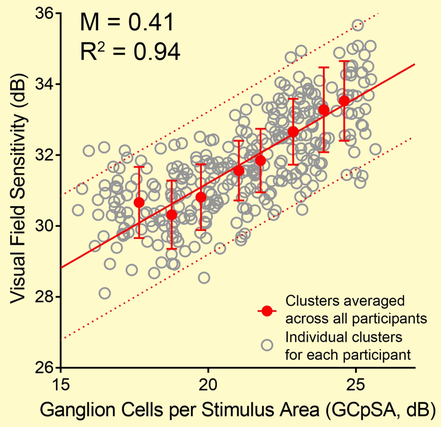

Figure 4.
Correlation and 95% predication intervals (dotted lines) allow accurate predication of visual field sensitivity from GCpSA calculated from GCL-IPL measurements.

Results and Discussion

This study leveraged off paradigms mapping spatially discrete ganglion cell structure-function correlations, thereby significantly improving capacity to differentiate age- and disease related loss.

- Retinal thickness measurements were precisely adjusted to spatially match functional data (**Figure 1**)
- For the first time, estimated number of ganglion cells was accurately derived from robust GCL-IPL measurements (**Figure 2**).
- GCL-IPL thickness measurements closely mirrored anatomically and functionally established patterns representing changes in ganglion cell number and/or density over time (**Figure 3**).
- Improved correlation between structure and function and narrow 95% predication interval with the current model allow early identification of patients at risk of functional deficits from easy accessible structural data (**Figure 4**).

Table 1. Patient data per decade

Cohort	n	Age	Gender*	Ethnicity^	OD:OS
20-29	29	25.5 ± 3.0	11:18	13:16:0	12:17
30-39	26	34.2 ± 3.0	9:17	11:15:0	15:11
40-49	69	45.8 ± 2.8	25:44	39:28:2	41:28
50-59	66	54.8 ± 2.8	30:36	42:20:4	37:29
60-69	40	64.0 ± 2.9	19:21	32:8:0	19:21
70-84	24	75.7 ± 4.5	15:9	19:4:1	8:16
All	254	50.3 ± 14.4	109:145	156:91:7	132:122

*Male:Female; ^Caucasian:Asian:Other; OD = right eye; OS = left eye

Conclusions

Spatially-temporally adjusted structural and functional measurements of the central GCL-IPL are highly concordant, providing a robust model of the normal macular structure-function relationship. This paradigm is directly transferable to current clinical instrumentation and provides a refined normative data range, thus facilitating earlier and more sensitive detection of glaucomatous damage. Furthermore, the current model allows the immediate prediction of localised visual function from structural imaging.

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[2]*Yoshioka N, Zangerl B, Nivison-Smith, et al. (2017) Pattern recognition analysis of age-related retinal ganglion cell signatures in the human eye. IOVS 58(7):3086-99.*