

Editorial

Perspectives on the use of frequency doubling and short wavelength perimetry for the diagnosis of glaucoma

Many will know Geoffrey Herbert Henry as a visual cortical physiologist. What many do not know is that Geoff started out life as an optometrist who abandoned his successful private practice to study the visual cortex. I came to work with Geoff at the Australian National University in 1987. My area of interest in those days was the real-time adaptation of visual cortical neurons to changes in image properties. Geoff introduced me to the concept of something called glaucoma. In 1989, after a cup of tea with Geoff, where the discussion had again centred on glaucoma, I had an idea that something called the spatial frequency doubling (FD) illusion might be useful in quantifying the well being of a real-time contrast gain-control system found in retinal ganglion cells that project to the Magnocellular LCN (M-cells),^{1,2} and that this might be a useful litmus test for glaucomatous neural damage. These M-cells have their sensitivity dynamically managed by the gain-control system. While M-cells are thought to contribute to our sensitivity to image motion, the computation of motion signals is done in the cortex, while the gain-control is retinal. I realized that the gain-control system could be the source of FD. A few weeks later I was faced with a glaucoma patient who with one eye could see a frequency doubling pattern on a display monitor but with the fellow eye saw the same screen as being completely blank. The subject had good reading vision and the pattern had a contrast of 100% so it seemed we were onto something.

By 1990³ I had confirmed that the low coverage factor of M-cells meant that detecting cell loss would be easier in that array, what Landers et al refer to as the redundancy theory.⁴ The concept is that it is easier to measure cell loss in arrays of ganglion cells that cover the retinal image sparsely. This idea also sold Welch Allyn (Skaneateles Falls, NY, USA) on the concept of using FD stimuli to diagnose glaucoma and they began to fund my research. After several patents,^{5,6} and great encouragement and assistance from Ivan Golberg in Sydney with clinical trials, the project (then known

internally in Welch Allyn as a 'Different Approach to Glaucoma Screening' or DAGS) was turned over to Chris Johnson in 1995. This was a good idea because Chris actually knew how to make a perimeter, the product of his ingenuity and collected wisdom being the frequency doubling technology (FDT) perimeter marketed by Humphrey-Zeiss (Dublin, CA, USA) since 1997. Among other things the above discussion should indicate to readers that I have a proprietary interest in the FDT perimeter and that my comments here should therefore be taken with a grain of salt. Readers are directed to another recent editorial for a more independent perspective.⁸

A previous comparative study of short wavelength automated perimetry (SWAP) and FDT showed good diagnostic concordance between these methods and less agreement between them and other perimetric techniques, including motion automated perimetry and achromatic automated perimetry (AAP).⁹ The good sensitivities of SWAP and FDT have been attributed to the low redundancy in the coverage of the retina by blue-on cells and Y-like magnocellular cells (MY-cells). The retinal ganglion cell coverage factor is the number of cells viewing each point in visual space. This is a product of cell density and the size of their individual receptive fields. Blue-on cells seem to be about 10% of all retinal ganglion cells projecting to the dorsal lateral geniculate nucleus (dLGN). There are perhaps half as many blue-off cells.¹⁰ The best evidence of low coverage factor for the cells subserving both FDT and SWAP comes from studies showing that these matrices of cells undersample the retinal image producing 'aliasing' effects.^{11,12} When cell arrays are not dense enough to capture the fine detail of the retinal image illusory images called 'aliases' are seen, hence the term 'aliasing'. This can be used to measure the cell density in the living eye.^{11,12} There is good evidence that the units subserving the FD illusion represent less than 2% of all ganglion cells and thus have a very low coverage factor.¹¹ Three other factors put FDT in good stead: low test-retest variability, tolerance of misrefraction, and the diagnostic significance of its mean defect statistic.

Test-retest variability of AAP is poor, growing rapidly with the depth of loss reported. Thus, a subject giving a 20 db loss at a point on one sitting has about a 50% chance of giving a normal reading on a subsequent sitting.¹³ This is an important point because it means that scotomas visualized with AAP should be regarded as regions of low reliability rather than as accurate measures of damage. Unlike

Footnote: The Australian National University (ANU) owns patents on the use of frequency doubling stimuli for the diagnosis of glaucoma. These patents are under license to Welch Allyn Ltd USA and are the basis for the FDT perimeter marketed by Humphrey Zeiss. Dr T Maddess derives royalty income from the licensed patents. The present work does not use the FDT perimeter but does compare it with other perimeters.

AAP the test-retest variability of FDT is not worse with depth of defect¹⁴ Short wavelength automated perimetry has recently been shown to have worse test-retest variability than AAP¹⁵ A further problem for SWAP is that yellowing of the lens with age would affect blue-on cell responses as they are antagonized by yellow Thus, the use of Landers et al of SWAP as the 'gold standard' may not have been the best choice In the long run the best approach would be to develop a multivariate diagnosis based on several measures and then examine correlations between SWAP FDT and other methods and that measure In either case practitioners should not expect great agreement between field losses reported by different perimeters or even between visits because glaucoma creates unreliable vision

Visual field unreliability in glaucoma was first noted by Heijl et al,¹³ and their findings with AAP, may be telling something about how FDT works Heijl et al. noted that variable AAP fields are the earliest sign of glaucoma. Of course, they might also be the earliest sign of an inattentive subject The point is what would make visual field sensitivity fluctuate, and can we tap into that? Recall that at the outset I mentioned that FD testing was designed to tap into the contrast gain control system of the M-cell pathway.^{1,2} This system drives the responsiveness of M-cells up and down on a timescale of 15 msec depending on the visual environment¹ If this system started to go wrong one would expect fluctuating sensitivity, so perhaps FDT is proving us with a measure of what Heijl et al reported that is less dependent on subject vigilance

As mentioned earlier, a benefit of FDT is that its low spatial frequency patterns are effectively defocused and therefore even refractive errors of up to ± 5 dioptres have little effect on the test outcome. Added to the low test duration for FDT, Landers et al say 4.5 min for FDT versus 11 min for SWAP, refractive tolerance makes the instrument ideal for screening Recent innovations mean full threshold FDT test times can probably be halved,¹⁶ and will improve the accuracy of the 90 s screening mode¹⁷

Like the test-retest variability, a surprising result for me has been that measures like the FDT mean defect⁷ are quite reliable diagnostics for glaucoma while the AAP mean defect is not Again it would seem that FDT is telling us something about the mechanisms related to the mechanism of glaucoma Some of the effects of intersubject variability can be minimized by comparison of the two eyes of one subject This has been demonstrated for FD stimuli⁷ but it probably applies as well for SWAP and AAP.

A vexing issue for some has been 'does the patient see FD at threshold and the related issue, 'isn't it just testing flicker', whatever that means This perspective is usually predicated on the idea that FD is based on a non-linearity. Many seem to think that all non-linearities get small at small signal strengths In fact, this is not always true. The non-linearity underlying FD¹⁸ and retinal ganglion cell gain control¹⁹ is rectification The visual nervous system treats bright and dark objects as having positive and negative contrasts, respectively The mechanism behind both FD and the gain

control is a rectifier in the sense that its response is proportional to the absolute value of this signed contrast. The reader will appreciate that taking the absolute value works down to zero. Thus, effects like FD, do not diminish with signal strength. Indeed, in humans FD is best seen at low contrasts²⁰

A complicating feature is the apparent fineness illusion²⁰ that affects our ability to judge the scale of patterns consisting of a sinusoidal grating summed with its second spatial harmonic For such stimuli the cortically perceived spatial frequency is intermediate between the fundamental and the harmonic pattern, whether the harmonic is real or illusory as in FD²⁰ It has long been known that some fundamental is still observable when FD is seen.¹⁸ If the FD signal weakens relative to the fundamental then the spatial frequency perceived at the cortex shifts. Thus, as we approach the contrast threshold for seeing ostensibly FD patterns (i.e. low spatial frequency, high temporal frequency), one might not expect humans to report a definite FD percept. Also, by definition, at threshold one only has a poor chance, typically 75%, of seeing anything at all, so it will be hard to answer this question. Our best data say that when subjects perceive any spatial frequency higher than the fundamental this indicates the presence of a percept shifting FD component. There is also evidence that low spatial frequencies outperform wide field flicker²¹ diagnostically.

So should we use FDT or SWAP? It seems to me that good statistical and clinical practice dictates that as many statistically independent sources of information as possible will, by definition, improve diagnosis. Short wavelength automated perimetry and FDT appear to test different retinal mechanisms so perhaps we should use both for a final diagnosis. For screening, FDT seems to have advantages. For long-term follow up it may be that the low test-retest variability of FD wins the day but we need more data to decide. Several labs are working on this so we may know soon. One thing is clear, given its very poor sensitivity and specificity, the day of the tonometer as the preferred rapid screening device is gone. In the words of another editorials 'FDT perimetry may finally be a tool that can cost-effectively screen populations at risk'.

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REFERENCES

- 1 Benardete EA, Kaplan E The dynamics of primate retinal ganglion cells *Visual Neurosci* 1999; 16: 344-68
- 2 Maddess T, Bedford S, James AC, Rose KA A multiple frequency, multiple region pattern electroretinogram: investigation of nonlinear retinal signals *Aust N Z J. Ophthalmol* 1997, 25: 94-7

- 3 Maddess T, Henry CH Density of nonlinear visual units and glaucoma. *Invest. Ophthalmol. Vis. Sci* 1990; 15(Suppl.): S230.
- 4 Maddess T, Henry CH. Nonlinear visual responses and visual deficits in ocular hypertensive and glaucoma subjects. *Clin. Vision Sci* 1992; 7: 371-83.
- 5 Maddess T. Method and apparatus for use in diagnosis of glaucoma. USA, 1991, Patent no 5 065 767.
- 6 Maddess T. Early detection of glaucoma. USA, 1995, Patent no. 5 912 723.
- 7 Maddess T, Goldberg-I, Wine S, Dobinson J, Welsh AH, James AC. Testing for glaucoma with the spatial frequency doubling illusion. *Vision Res* 1999; 39: 4258-73.
- 8 Alward WLM. Editorial: Frequency doubling perimetry for the detection of glaucomatous field loss. *Am. J Ophthalmol* 2000; 129: 376-8.
- 9 Sample PA, Bosworth CF, Lee BL, Perez JS, Weinreb RN. Comparison of standard, short-wavelength, frequency doubling and motion perimetry in eyes with glaucomatous optic neuropathy. *Invest. Ophthalmol. Vis. Sci* 1998; 39: S656.
- 10 Lee BB. Receptive field structure in the primate retina. *Vision Rts* 1996; 36: 631-44.
- 11 Maddess T, Hemmi J, James AC. Evidence for spatial aliasing effects in the Y-like cells of the magnocellular visual pathway. *Vision Rts* 1998; 38: 1843-59.
- 12 Williams DR, Sekiguchi N, Brainard D. Color, contrast sensitivity, and the cone mosaic. *Proc. Natl Acad. Sci. USA* 1993; 90: 9770-7.
- 13 Heijl A, Lrindgren A, Lrindgren G. Test-retest variability in glaucomatous visual fields. *Am J Ophtbalmol* 1989; 108: 30-5.
- 14 Chauhan BC, Johnson CA. Test-retest variability of frequency-doubling perimetry and conventional perimetry in glaucoma patients and normal subjects. *Invest Ophthalmol Vis Sci* 1999; 40: 648-56.
- 15 Blumenthal EZ, Sample PA, Zangwill L, Lee AC, Kono Y, Weinreb RN. Comparison of long-term variability for standard and short-wavelength automated perimetry in stable glaucoma patients. *Am J Ophthalmol* 2000; 129: 309-13.
- 16 Cello KE, Nelson-Quigg JM, Johnson CA. Frequency doubling perimetry for detection of glaucomatous field loss. *Am J Ophthalmology* 2000; 129: 314-22.
- 17 Patel SC, Friedmann DS, Varadkar P, Robin AL. Algorithm for interpreting the results of frequency doubling perimetry. *Am J Ophtbalmol* 2000; 129: 323-7.
- 18 Kelly DH. Nonlinear visual responses to flickering sinusoidal gratings. *J Opt Soc Am* 1981; 71: 1051-5.
- 19 Victor JD, Shapley RM. The nonlinear pathway of Y ganglion cells in the cat retina. *J Gen Physiol* 1979; 74: 671-89.
- 20 Maddess T, Kulikowski JJ. Apparent fineness of stationary compound gratings. *Vision Rts* 1999; 39: 3404-16.
- 21 Maddess T, Severt WL. Testing for glaucoma with the frequency doubling illusion in the whole, macular and eccentric visual fields. *Aust NZ J Ophtbalmol* 1999; 27: 198-200.