

Sensitivity and Specificity of Frequency Doubling Perimetry in Neuro-ophthalmic Disorders: A Comparison with Conventional Automated Perimetry

Michael Wall,^{1,2} Richard K. Neabring,¹ and Kimberly R. Woodward¹

PURPOSE. Frequency-doubling technology (FDT) perimetry was developed as a screening test for glaucoma. Patients with damage to the neuro-ophthalmic sensory visual pathways have different patterns of visual loss than patients with glaucoma. The current study was designed to determine the sensitivity and specificity of FDT as a screening test, compared with conventional automated perimetry (CAP) in neuro-ophthalmic disorders and to test the extent to which it may isolate the M_y cells.

METHODS. FDT and CAP were performed in 97 patients with sensory neuro-ophthalmic disorders and 42 subjects from the general population. The total and pattern-deviation probability plots for test loci common to the two perimetric tests were compared. The gold standard was an unequivocal clinical diagnosis.

RESULTS. The sensitivity of FDT was 81.3%, with a specificity of 76.2%. The difference in sensitivity and specificity of CAP, 87.5% and 81.0%, respectively, was not statistically significant (by χ^2 test). In subjects with optic neuropathies, the similarity of the defect shown on FDT and CAP was judged good or fair in 62 of 72 cases. The extent of the defect as seen with FDT and CAP was equal in 41 of 72 cases, more extensive with FDT in 12, and more extensive with CAP in 19. In the patients with hemianopia, scattered abnormal test locations with FDT testing masked the hemianopic nature of the defect in 15 of 25 patients. Also, test locations along the vertical midline in densely hemianopic areas were seen with FDT testing in some patients with hemianopia, probably due to light scatter across the vertical midline and into the uninvolved hemianopic field.

CONCLUSIONS. FDT has sensitivity and specificity similar to that of CAP for detecting visual field defects in patients with optic neuropathies. However, defects in patients with hemianopias may be missed because of the presence of scattered abnormal test locations and failure to detect test locations along the vertical meridian. The defects demonstrated by both tests in patients with optic neuropathies are similar in number, extent, and shape of the defects. This suggests FDT may not be isolating the magnocellular (M) cells with nonlinear responses to stimulus contrast (M_y cells) in patients with visual loss. (*Invest Ophthalmol Vis Sci.* 2002;43:1277-1283)

From the Departments of ¹Ophthalmology and ²Neurology, College of Medicine, University of Iowa, Iowa City, Iowa.

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Corresponding author: Michael Wall, Department of Neurology, University of Iowa, College of Medicine, 200 Hawkins Drive 2007 RCP, Iowa City, IA 52242-1053; michael-wall@uiowa.edu.

The frequency-doubling illusion occurs when a low-spatial-frequency sinusoidal grating undergoes high-frequency counterphase flicker, giving the appearance of a spatial frequency twice that of the actual spatial frequency.¹ The frequency doubling technology (FDT) method is based on the assumption that the low spatial frequency of the grating in combination with the high temporal frequency of the counterphase flicker of the stimulus preferentially stimulates cells of the magnocellular (M) layer of the lateral geniculate nucleus.^{2,3} These M cells are believed to be primarily involved in the detection of motion and rapid flicker (although the parvocellular [P] cells also play a role in motion detection).^{4,5}

The frequency-doubling percept has been attributed to a nonlinear response to contrast. The M-cell subset with nonlinear responses to stimulus contrast, the M_y cells, account for a small fraction of the total number of M cells. If the FDT method isolates these cells, a population of cells is tested that may have little anatomic and physiologic redundancy, although the amount of receptive field overlap of the M_y system is unknown. If there is not substantial overlap, there is probably not much redundancy, and visual system damage might be expected to show visual field defects early in a pathologic course. However, because subjects respond, whether or not they see the illusion, it is not clear whether this subset of M cells or the M cells, per se, are isolated.

FDT perimetry was developed for screening patients for evidence of glaucomatous damage to the optic nerve. It has been validated thoroughly for this purpose in normal subjects and in those with glaucoma.^{6,7} As a glaucoma-screening device, the sensitivity of FDT perimetry is similar to that of conventional automated perimetry (CAP), and its specificity is excellent.^{2,6,8-11} However, patients with nonglaucomatous damage to the optic nerve or damage to the optic chiasm or retrochiasm pathways may have very different visual field defect morphology than patients with glaucoma. For example, patients with optic neuritis, anterior ischemic optic neuropathy, or compressive optic neuropathies may have cecocentral loss, in addition to arcuate nerve fiber bundle-like defects.

Patients with hemianopic defects present a different problem, in that those defects are considerably different from glaucomatous ones. First, in patients with hemianopias, the visual field defects usually respect the vertical midline. Therefore, if a stimulus is placed too close to the vertical meridian, with light scatter or fixation shifts, the procedure may fail to detect damage tested by locations along the vertical meridian. Second, defects in patients with hemianopias may be small with steep slopes, compared with the usually shallow-sloped defects in patients with glaucomatous visual field damage. Third, the defects have a homonymous character, occurring in approximately the same test locations in each eye. It is necessary that this homonymous character be obvious when examining test results. Because of these differences and the now widespread use of FDT perimetry as a general visual screening device, we undertook this study to determine whether FDT perimetry is sensitive as a screening test in patients with sensory neuro-ophthalmic disorders.

A secondary purpose was to test the hypothesis that by isolating the M_y cells, FDT perimetry would be a more sensitive test than CAP for the reasons just stated. If there is isolation of the M_y cell by FDT and the disease process damages the M cells more than the P cells (as suggested in idiopathic intracranial hypertension and optic nerve compression^{12,13}), FDT-detectable defects should occur earlier and be more extensive. Alternatively, if the reduced redundancy hypothesis is true,¹⁴ and if there is not much redundancy in the M_y system, the sensitivity of FDT perimetry should be substantially higher than that of CAP.

METHODS

Subjects

Ninety-seven patients with neurologic disorders causing visual loss gave informed consent to participate in the study, as did 42 normal subjects. The University of Iowa's Institutional Review Board approved the protocol, which adhered to the tenets of the Declaration of Helsinki. To recruit normal subjects, phone calls were placed to people identified at random from the Iowa City telephone book, in which they were asked participate. We used this "population-based" control instead of ocularly normal subjects because our goal was to determine the sensitivity and specificity of FDT in neuro-ophthalmic disorders as would occur in a general screening situation. The patients were all seen in the University of Iowa Hospitals and Clinics' Neuro-ophthalmology Clinic. Twenty-nine had anterior ischemic optic neuropathy by the Ischemic Optic Neuropathy Decompression Trial criteria,¹⁵ 16 met the Dandy criteria¹⁶ for idiopathic intracranial hypertension, 4 had compressive optic neuropathy documented by neuroimaging, and 23 had optic neuritis, by the criteria of the Optic Neuritis Treatment Trial.¹⁷ The mean age of the patients was 46.6 ± 16.8 years (range, 21–80) and of the normal subjects was 44.9 ± 18.9 years (range, 20–81). The default field for new patients in our neuro-ophthalmology clinic is Goldmann perimetry; therefore, the subjects' diagnosis, when visual field criteria were necessary, was based on Goldmann perimetry results in most cases. Also, as can be seen in the results, some patients with optic neuropathy had normal results with CAP. Therefore, abnormal CAP findings were not necessary for subjects to be included in the study. All subjects underwent neuro-ophthalmic examination, including intraocular pressure measurement. Patients had lesions, documented by magnetic resonance imaging or computed tomography, which showed damage to the chiasmal or retrochiasmal visual system, or they had objective evidence of an optic neuropathy. They all had perimetry with a field analyzer (program 24-2, or in the case of the patients with temporal lobectomies, program 30-2; Humphrey Systems, San Leandro, CA) and FDT perimetry (C-20 threshold) performed in both eyes on the same day. The normal subjects and patients with optic neuropathy had one eye tested. The patients with hemianopia had two eyes tested.

Perimeters

CAP was performed with a visual field analyzer (Humphrey) according to the manufacturer's recommendations. We used a 4-mm² Goldmann size III stimulus (0.43°) on a dim background (31.5 apostilb). The differential light sensitivity threshold was found at each test location. The patients' appropriate near correction was used. Rest breaks were allowed when requested. The 24-2 or 30-2 test program (Humphrey) presents stimuli on a 6° spaced grid encompassing the central 21° or 27° of the visual field.

FDT perimetry was performed after conventional perimetry testing with at least a 15-minute rest period between, in an attempt to diminish the fatigue effect. Testing was performed in a darkened room (the test can be taken with normal room lighting) using an FDT device (FDT threshold C-20 test, version 2.6; Welch-Allyn; Skaneateles, NY). This protocol determines the minimum contrast necessary to detect the stimulus for each of the 17 target locations in the stimulus display (Fig.

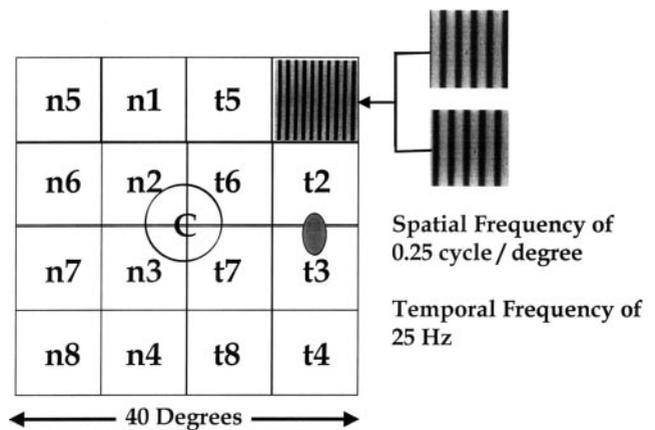


FIGURE 1. A 25-Hz alternating sinusoidal contrast grating stimulus used in FDT, demonstrating the 10° in diameter test locations.

1). This is accomplished by means of a staircase bracketing procedure. If a stimulus is detected, the contrast is decreased for the next presentation; if the stimulus is not detected, contrast is increased. FDT perimetry uses a modified binary search (MOBS) type of staircase. The FDT software tabulates the status of each MOBS staircase result for the individual stimulus locations and signals the end of the test when all are completed. That is, the test continues until the stimulus with the least contrast is detected at each test location. The test time for the C-20 procedure is approximately 4 minutes per eye.

Stimulus presentation time is a maximum of 720 ms. During the first 160 ms, stimulus contrast is increased gradually from zero. If the stimulus is not seen, the display shows this maximum contrast for the trial for a variable random interval ranging between 200 to 400 ms. The contrast is then gradually decreased to zero during the final 160 ms. If the stimulus is seen, the stimulus presentation is interrupted when the response button is pushed. After each stimulus presentation, there is a variable random interval of 0 to 500 ms to minimize anticipation by the patient. Responses that fall outside a 1000-ms response window are not counted.

With the C-20 stimulus presentation pattern, 17 stimulus locations are tested. This pattern has four stimulus test locations in each quadrant, each approximately 10° in diameter, and a central 5° radius target. This provides a test area of approximately 40° × 40° or a 20° radius surrounding fixation. It is by far the largest stimulus size commonly used in clinical perimetry.

Visual Field Defects

To qualify as a visual field defect for CAP, three adjacent abnormal points at the $P < 0.05$ level or two adjacent points with one abnormal at the $P < 0.01$ level were needed. The defects also must occur in a clinically suspect area. For data using FDT perimetry, to meet criteria for a visual field defect, we required two adjacent abnormal points at $P < 0.05$ or one homonymous point with a probability of occurrence in a normal population of less than 1%. The abnormalities had to appear in a clinically suspect area. We also required that, to qualify as a hemianopic defect, the abnormal test points be along the vertical meridian and homonymous and that there not be other abnormal test locations that would obviously obscure the homonymous pattern. That is, there had to be a reasonable minimum of scattered abnormal test locations from noninvolved (normal hemifield) test locations to be able to clearly see the hemianopia. We did not accept a single abnormal test location as a visual field defect in one eye, because with 17 test locations, one abnormal test location would be expected to occur, by chance alone.

Data from the patients' total-deviation probability plots and pattern-deviation plots were separately analyzed for normal subjects, patients with optic neuropathy, and patients with hemianopias. Lastly, the test

TABLE 1. Sensitivity and Specificity of (CAP) and FDT Perimetry in Patients with Nonglaucomatous Optic Neuropathies

	CAP	FDT	P
Total deviation			
Sensitivity	86.1	77.8	0.28
Specificity	81.0	76.2	
Pattern deviation			
Sensitivity	84.7	79.2	0.52
Specificity	76.2	61.9	
All information			
Sensitivity	84.7	79.2	0.12
Specificity	76.2	61.9	

Probabilities are by χ^2 testing for differences between the methods.

results were analyzed using all the data supplied (including the total-deviation probability plots and pattern-deviation plots), as a clinician would for a screening visual field test.

For the total-deviation probability plot and pattern-deviation plot analyses, we compared the extent of the defects using the tests' total and pattern-deviation probability plots. If the defects' extent was more than 25% more in area, that perimetric examination was tabulated as showing a more extensive defect in that patient. Otherwise, the extent was tabulated as the same. We also judged the similarity of the topographic pattern of the visual field defects. The similarity was categorized as good when the same type of defect was present in both, fair when the defects were different but some overlap was present, and poor when the areas of visual loss did not coincide.

Statistical Analysis

Sensitivity and specificity measures were calculated in the traditional manner. The gold standard for classification of disease was the patient's clinical diagnosis. The χ^2 and Fisher exact tests were used to test for differences between groups (FDT and CAP).

RESULTS

Of the 42 subjects randomly selected from the general population who agreed to be tested, 8 (19%) had visual field defects with program 24-2 testing and 10 (23%) with FDT perimetry. Findings in both tests were abnormal in three subjects. Two patients had elevated intraocular pressures but had normal test results with both perimetry tests.

We found the sensitivity of FDT in all patients to be 81.3%, with a specificity of 76.2%. The sensitivity of CAP was 87.5%, with a specificity of 81.0% (NS, χ^2).

We then divided the patient sample into those with optic neuropathies and those with hemianopias. The sensitivity and specificity results are found in Tables 1 and 2. Of the patients with optic neuropathies, 62 (86%) of 72 had visual field defects, with the total-deviation probability plot results by conventional perimetry and 56 (78%) by FDT. The results of the pattern-deviation tabulation were 61 (85%) with CAP and 57 (79%) with FDT. All patients with anterior ischemic optic neuropathy had characteristic visual field defects to both total and pattern-deviation plot analyses, except one patient who had normal results with both tests and one patient with a cecentral defect by CAP testing who had normal FDT results. Patients with compressive optic neuropathies had similar results with total and pattern-deviation probability plot analyses. Three of the four patients had characteristic visual field defects. Eleven (62.5%) of 16 patients with idiopathic intracranial hypertension had defects with both CAP testing and FDT with total-deviation probability plot analysis. Pattern-deviation analysis revealed 62.5% and 69% respectively. Of the 23 patients

TABLE 2. Sensitivity and Specificity of CAP and FDT Perimetry to Detect Any Visual Field Defect in Patients with Hemianopia

	CAP	FDT	P
Total Deviation			
Sensitivity	92.0	48.0	0.002
Specificity	81.0	76.2	
Pattern Deviation			
Sensitivity	100.0	48.0	<0.001
Specificity	76.2	61.9	
All information			
Sensitivity	96.0	24.0	<0.001
Specificity	81.0	76.2	

Note the data from the interpretation performed as would a clinician, using the probability plot data and all information available (bottom). Many FDT defects were missed because scattered abnormal test locations obscured the hemianopia pattern.

with optic neuritis, 87% had defects shown in the total-deviation plot analysis whereas 78% had defects with FDT. In this group, the sensitivity for the pattern-deviation plot analysis were 70% for CAP testing and 65% for FDT.

The results in the patients with hemianopias present quite a different story (Table 2). Simply evaluating whether the 25 patients (50 visual field examinations) had total-deviation plot defects (hemianopic character or not) revealed 48 of 50 examinations had results showing defects with CAP testing, whereas 41 of 50 results were abnormal with FDT. For the pattern-deviation plot analysis, all CAP examinations had abnormal results, whereas 45 of 50 FDT results were abnormal.

Most revealing was the clinical interpretation that was performed as if the patient were having a visual field screening test performed as part of a patient visit. Although there were no meaningful differences in the patients with optic neuropathy, there were large differences in the patients with hemianopia (Table 2). There were two factors that appeared to be causing hemianopic defects to be missed. First, there were numerous scattered abnormal test locations with FDT testing that masked the hemianopic nature of the defect (15/25 patients). Second, the main reason for failure to demonstrate hemianopic defects in three patients was that test stimuli along the vertical midline related to the hemianopic field were seen at the non-hemianopic vertical test locations likely due to either light scatter across the vertical or shifts in fixation. Another apparent factor was that homonymous hemianopic defects could more easily be seen with the Humphrey gray-scale graphic than with the probability plots. No gray-scale graphic is provided with FDT.

The analysis for extent and similarity of visual field defects is found in Table 3. Often, especially in the patients with optic

TABLE 3. Comparison of the Extent (same extent, CAP program 24-2, or FDT at least 25% greater) and Similarity of Defects

Group	Extent of Defect (n)	Similarity of Defects (n)
Optic neuropathy	Same (41)	Good (39)
	24-2 (19)	Fair (23)
	FDT (12)	Poor (10)
Hemianopia	Same (6)	Good (5)
	24-2 (15)	Fair (11)
	FDT (4)	Poor (9)
All patients	Same (47)	Good (44)
	24-2 (34)	Fair (34)
	FDT (16)	Poor (19)

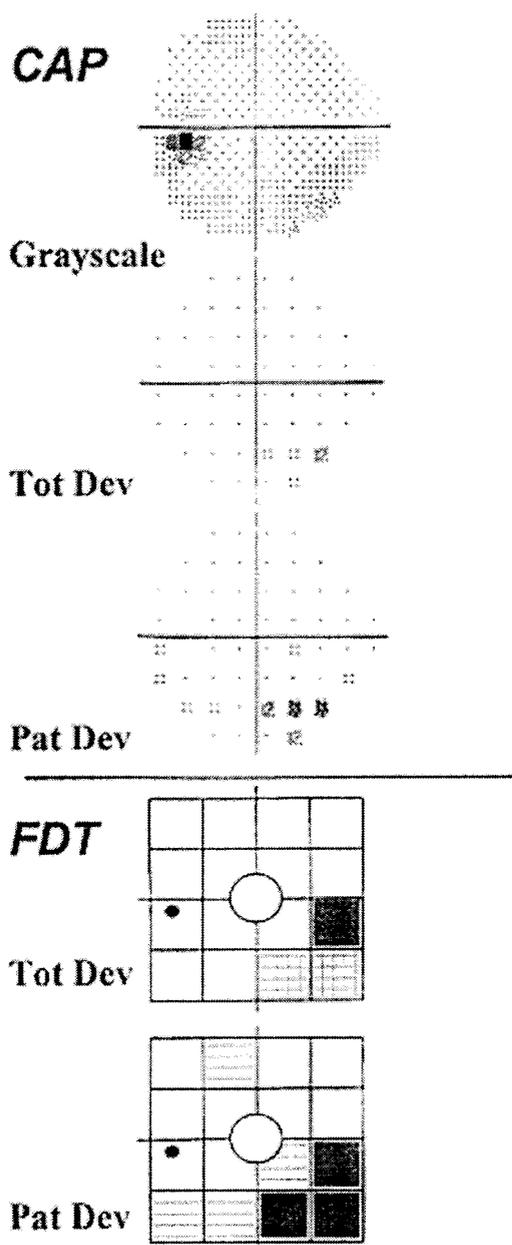


FIGURE 2. A 21-year-old woman with idiopathic intracranial hypertension had an inferior arcuate defect well delineated on both tests.

neuropathy, there was excellent agreement between the results of the two tests. For example, Figure 2 shows the results in a patient with idiopathic intracranial hypertension. The inferior arcuate defect was shown similarly by both testing procedures. Figure 3 shows results in a patient with anterior ischemic optic neuropathy who had a cecocentral scotoma present with CAP; FDT results were normal. A 28-year-old woman with idiopathic intracranial hypertension (Fig. 4) had a large inferior arcuate defect present on CAP. The defect was present and more extensive on FDT perimetry. A 53-year-old woman with a temporal lobectomy for control of epilepsy had a right superior homonymous hemianopia present on both tests (Fig. 5). A 78-year-old man with a left occipital stroke had a congruous, macula-sparing, right inferior quadrantanopia present on CAP testing (Fig. 6); FDT perimetry showed some loss in the same area but scattered abnormal test locations obscured the hemianopic morphology of the visual field de-

fect. A 76-year-old man had incongruous right homonymous hemianopia (Fig. 7). FDT perimetry did not show the abnormality along the vertical meridian on the right side, because of light scatter or fixation shifts.

DISCUSSION

FDT is a method designed to isolate and specifically test the function of the M_y subset of retinal ganglion cells. This may be important for two reasons. Because the M-cell system has fewer fibers, it may have less redundancy. (However, the receptive field overlap of the M_y system is unknown, and sub-

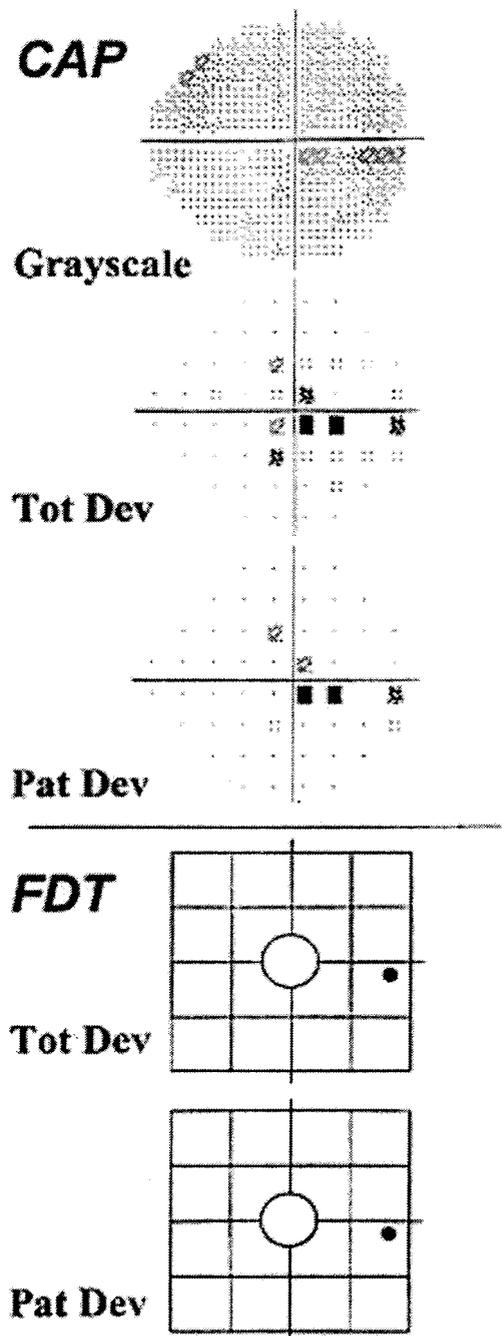


FIGURE 3. A 65-year-old man with anterior ischemic optic neuropathy had a cecocentral scotoma on testing with CAP. FDT results were normal.

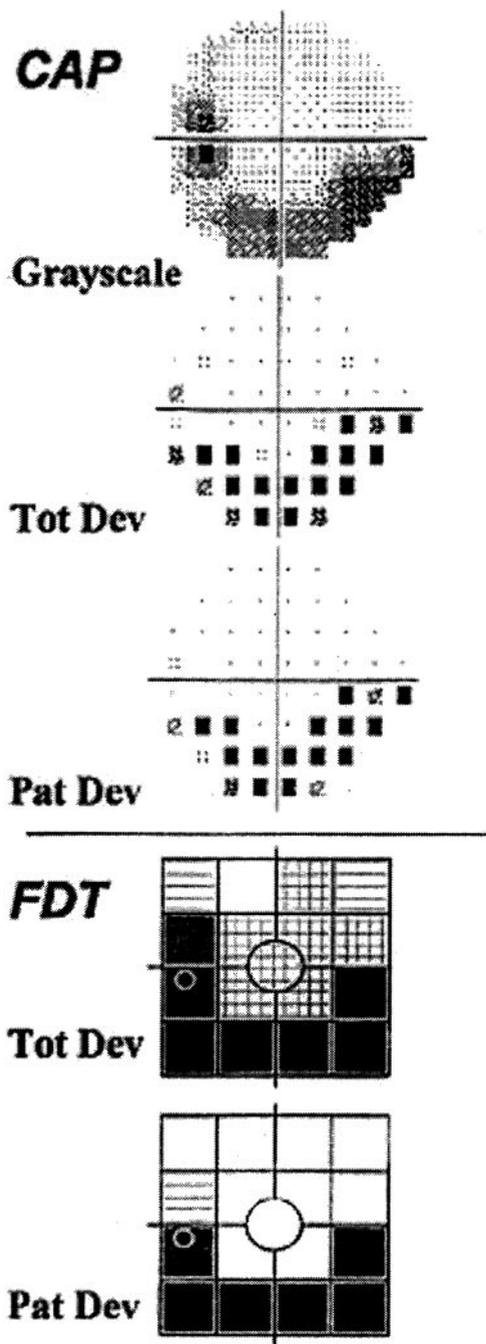


FIGURE 4. A 28-year-old patient with idiopathic intracranial hypertension had an inferior arcuate defect seen on CAP and FDT perimetry. FDT also showed more extensive generalized loss on the total-deviation probability plot.

stantial overlap may negate the effect of having fewer fibers.) If there is less redundancy, there should be less tolerance to optic nerve damage.¹⁴ and visual field loss should evolve early in the course of optic nerve damage. Therefore, it has been hypothesized that testing for the detection of the frequency-doubling illusion should be a very sensitive method of identifying early visual field loss.

Alternatively, there is evidence that there may be selective large retinal ganglion cell type loss in glaucoma¹⁸⁻²⁰ and, possibly, idiopathic intracranial hypertension.^{12,13} If the M_y cells are selectively lost, the visual field deficit may occur, because the spared cells of other types cannot easily detect the

stimulus. Therefore, there is a second theoretic basis that psychophysically isolating the M_y cell for perimetry may allow for early detection of visual loss.

In the current study, FDT was similar in sensitivity and specificity to CAP in patients with optic neuropathies. The shape of the field defects demonstrated by both perimetric methods were similar. Similarly, the extent of the abnormality, on average, appeared to be similar between the two tests. Therefore, if the M_y cell is being isolated, it does not appear to result in an increase in the sensitivity of FDT perimetry.

There are many investigations of sensitivity and specificity comparing FDT and CAP in glaucoma.^{7-10,21} The studies are difficult to compare because (1) different criteria for abnormality were used; (2) full threshold testing was performed in some studies, whereas the fast screening protocols were used in others; (3) population-based normal subjects were used in some studies, whereas ocular normal subjects were used in others; and (4) samples of varying degrees of glaucoma were reported. Of the five studies listed, the sensitivity of FDT and

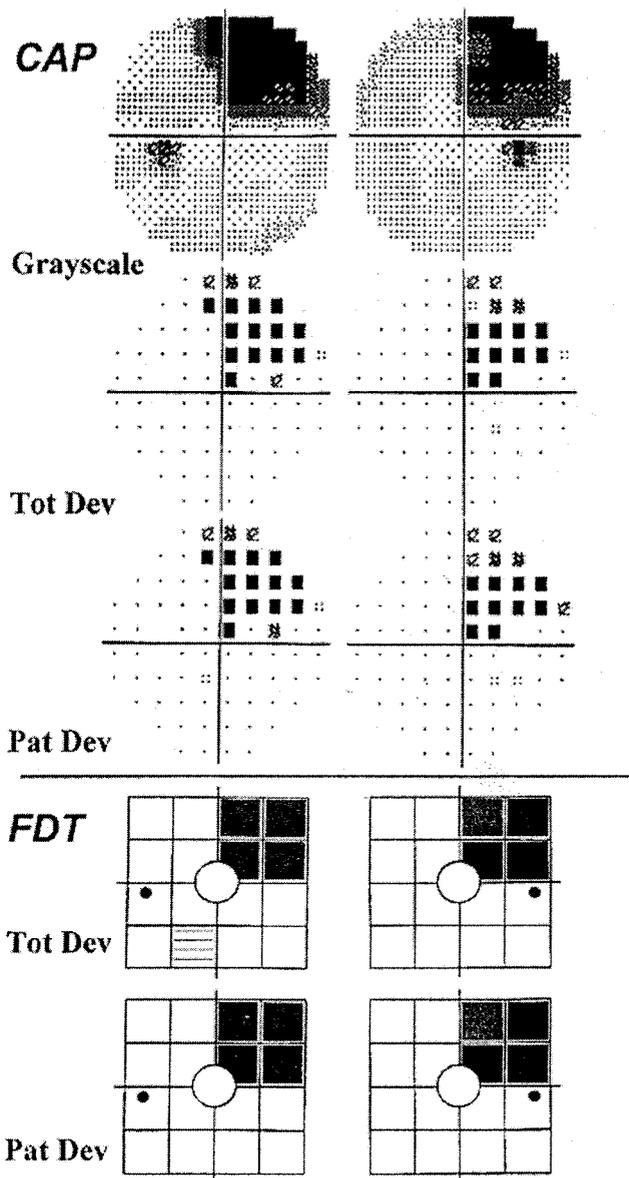


FIGURE 5. A 53-year-old woman with a temporal lobectomy for epilepsy control had a right superior homonymous quadrantanopia seen well with both CAP and FDT perimetry.

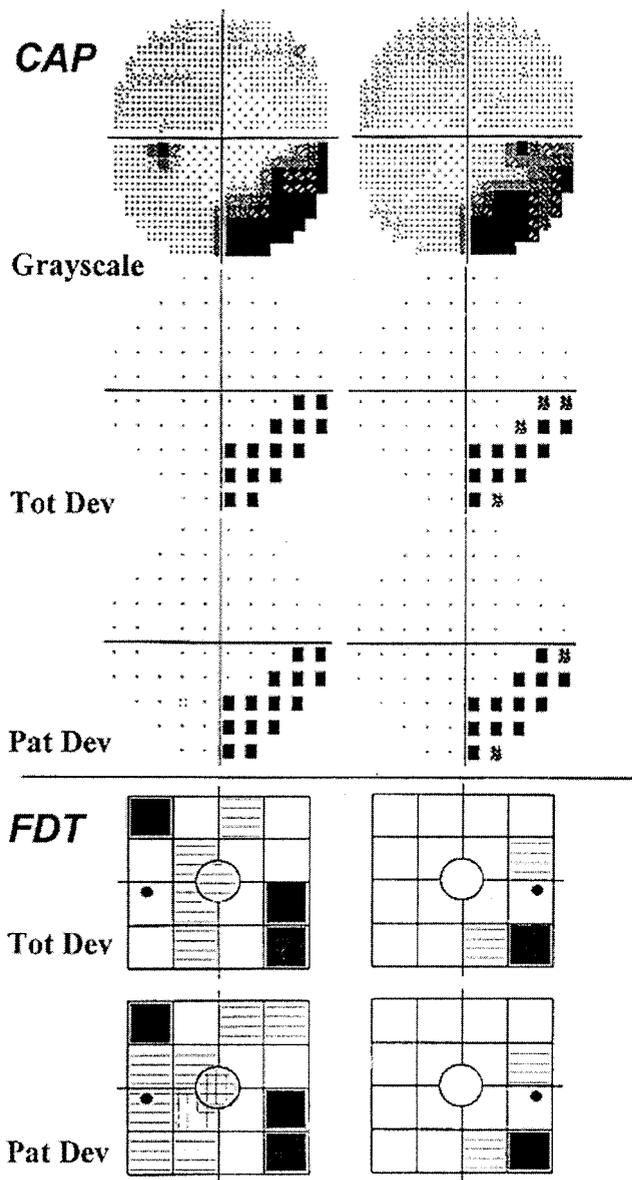


FIGURE 6. A 78-year-old man had a macula-sparing congruous, right inferior homonymous hemianopia, due to a left occipital stroke, shown by CAP. The defect was present on FDT, but noise from scattered abnormal test locations obscured identification of the homonymous hemianopia.

CAP appear equivalent in four. A study by Sample et al.,²¹ in which criteria were set for a variety of tests at a specificity of 90% and the test results compared, showed FDT to be more sensitive in patients with glaucomatous optic neuropathy. Our results show that there is no improvement in sensitivity for FDT over CAP for nonglaucomatous optic neuropathies, and it is controversial whether there is improvement in glaucoma detection. Therefore, we conclude it is unlikely that the M_y cell is being psychophysically isolated in FDT perimetry.

To date, the only report of FDT testing in patients with neurologic disease is by Fujimoto and Adachi-Usami.²² They reported results in 14 patients with recovered optic neuritis. They compared deficits by zone (central, paracentral, and peripheral) and found deficits with both CAP and FDT. With CAP, eight patients had normal findings and six had localized defects by Optic Neuritis Treatment Trial criteria. They did not report the FDT results in individual eyes. Ours is the first report

of other nonglaucomatous optic neuropathies and hemianopias.

It is clear that FDT perimetry (version 2.60; Welch-Allyn) failed to detect hemianopias in a substantial number of patients. A variety of mechanisms is likely to be responsible for this. An important consideration is scatter of light from the stimulus from the nonseeing into the seeing hemifield. Clearly, test locations along the vertical in a densely hemianopic field can be missed with FDT. We have tested a group of six subjects with a version of FDT where the stimulus was offset 2° away from the vertical without improvement in the results. Testing with a 3° offset improved the results. This experiment is the subject of another article currently in preparation. Another potential reason for this failure to detect test locations is shifts in fixation. In any event, this problem can be mostly resolved with a change in the FDT stimulus size and placement.

A problem that is more difficult to remedy is the presence of scattered abnormal test locations obscuring the homonymous hemianopic character of the defect (Fig. 6). The reason for the presence of this probability plot noise is unclear. It can also occur in CAP, but because there are at least 52 test

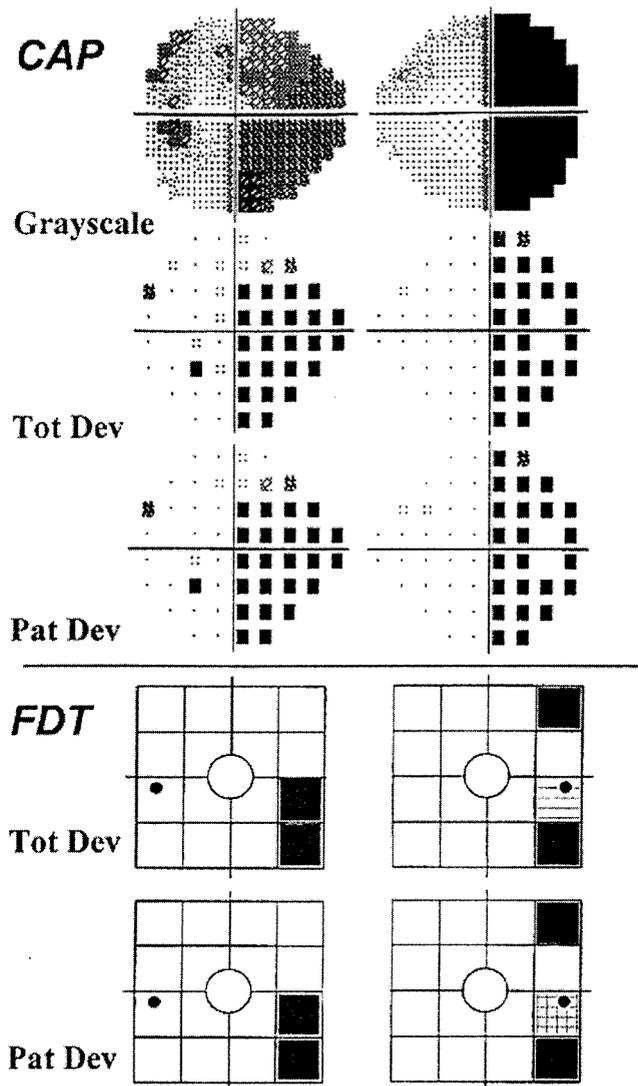


FIGURE 7. In a 76-year-old man with an incongruous right homonymous hemianopia due to a left occipital stroke, CAP detected all stimuli along the vertical in the hemianopic visual field, but FDT perimetry failed to show the defect along the vertical midline.

locations, the effect of a few scattered abnormal test locations is much less problematic (Fig. 7). A possible explanation is that FDT perimetry was performed after CAP. However, all patients had at least a 15-minute break, and most had a much longer break between the tests.

Although the gray-scale printout, when used exclusively, can lead to diagnostic errors,²³ it can also be useful in selected instances. For example, the four superior-edge test locations used in CAP with a 6° spaced grid have a very high variability because of interference by the lids and eye lashes. Subtle bitemporal hemianopias, present on the gray-scale printouts, can be missed if only the probability plots are used for those test locations. In all our patients, the hemianopias were obvious on the gray scale. It would probably be useful if this graphic representation were available on FDT perimetry.

In summary, we found FDT and CAP to have similar specificities and sensitivities in patients with nonglaucomatous optic neuropathies. In addition, the abnormalities found were of similar appearance and extent. This suggests the FDT stimulus does not adequately isolate the M_y cells, nor is it likely that the test method would be more sensitive than CAP. Patients with hemianopias present another problem. There is failure to identify hemianopic defects because of detection of the stimulus by the receptive fields of the uninvolved hemifield and the presence of scattered abnormal test locations. In conclusion, however, we found FDT perimetry to be an excellent visual field screening test for nonglaucomatous optic neuropathies. The addition of a gray-scale printout and a change in the position, size, and number of stimuli appear to be needed for FDT to function as well as CAP for detection of hemianopias.

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