

Frequency-doubling technology perimetry and multifocal visual evoked potential in glaucoma, suspected glaucoma, and control patients

Fabio N Kanadani¹
Paulo AA Mello¹
Syril K Dorairaj²
Tereza CM Kanadani³

¹Federal University of Sao Paulo, Sao Paulo, Brazil; ²Mayo Clinic, Department of Ophthalmology, Jacksonville, Florida, USA;

³Sao Jose University Hospital, Belo Horizonte, Brazil

Introduction: The gold standard in functional glaucoma evaluation is standard automated perimetry (SAP). However, SAP depends on the reliability of the patients' responses and other external factors; therefore, other technologies have been developed for earlier detection of visual field changes in glaucoma patients. The frequency-doubling perimetry (FDT) is believed to detect glaucoma earlier than SAP. The multifocal visual evoked potential (mfVEP) is an objective test for functional evaluation.

Objective: To evaluate the sensitivity and specificity of FDT and mfVEP tests in normal, suspect, and glaucomatous eyes and compare the monocular and interocular mfVEP.

Methods: Ninety-five eyes from 95 individuals (23 controls, 33 glaucoma suspects, 39 glaucomatous) were enrolled. All participants underwent a full ophthalmic examination, followed by SAP, FDT, and mfVEP tests.

Results: The area under the curve for mean deviation and pattern standard deviation were 0.756 and 0.761, respectively, for FDT, 0.564 and 0.512 for signal and alpha for interocular mfVEP, and 0.568 and 0.538 for signal and alpha for monocular mfVEP. This difference between monocular and interocular mfVEP was not significant.

Conclusion: The FDT Matrix was superior to mfVEP in glaucoma detection. The difference between monocular and interocular mfVEP in the diagnosis of glaucoma was not significant.

Keywords: standard automated perimetry, electrophysiology, glaucomatous eyes

Introduction

Open-angle glaucoma (OAG) is a chronic progressive disease, characterized by typical changes of the optic nerve head and retinal nerve fiber (RNFL) layer, with correlated visual field defects.¹

The OAG is accompanied, in most cases, by elevated intraocular pressure (IOP).² This elevated IOP is the most important risk factor for the development of the disease.¹ Other known risk factors are older age, African ethnicity, myopia, family history of diabetes³⁻⁵ and thin central corneal thickness.⁶

The diagnosis of OAG classically has been based on the observation of changes on the optic nerve head and RNFL associated with corresponding visual field defects in the presence or not of statistically altered IOP.²

Ganglion cell types

There is evidence that the ganglion cells can also be divided according to their anatomical and functional characteristics.^{7,8} The P cells are classified as type I when they have small axons with slow conduction and high spatial and low temporal frequency. The loss of these cells can be detected particularly well by high-pass

Correspondence: Fabio Nishimura Kanadani
Federal University of Sao Paulo,
Rua Gonçalves Dias 89, sl 601, Belo
Horizonte, MG, Brazil 30140-090
Email fkanadani@gmail.com

resolution perimetry. The type II P cells have large axons; their conduction is slower than the type I, and they are sensitive to blue stimulus. The loss of these cells may be better detected by blue-yellow chromatic perimetry. The type III M cells have large axons and fast conduction, and they are sensitive to low spatial and high temporal frequency. A particular subset of M cells, My, are those capable of conducting this stimulus. These cells constitute a small portion of the M cells, approximately 20%, which corresponds to 3%–5% of the total number of fibers. These cells can be best detected by frequency-doubling perimetry (FDT).

Standard automated perimetry

Standard automated perimetry (SAP) is the gold standard for the functional evaluation. The analysis of visual fields is based on the patient's perception of bright spots projected on a white background. This technique has some limitations – it depends on patient participation, has fluctuation sensitivity, and the defect it evaluates is usually not associated with an early diagnosis of glaucoma.⁹ Kerrigan-Baumrind et al¹⁰ reported that the patient must have a loss between 25% and 35% of retinal ganglion cells to find a statistical significance defect in SAP.

Frequency-doubling perimetry

The FDT presents stimuli in a field formed by a square of 10° with black and white bands that alternate following a sinusoidal pattern, a (low) spatial frequency of 0.25 cycle/degree, and a (high) temporal frequency of 25 Hz.¹¹

Although controversial, the FDT has been described by some authors as a technique capable of detecting functional defects earlier than SAP.^{12,13} It is believed that this technique stimulates a specific subset of ganglion cells that have a broad axon defined as My cells.^{14,15} The stimulus of a cell subset would lead to a better sensitivity than SAP by the theory of cellular redundancy described by Johnson et al.¹⁶ In this description, distinct cell subsets overlap in anatomical layers so that even if there was a localized loss of some cell subset, the region would respond to some kind of stimulus.

FDT Matrix

The latest generation of FDT, the Matrix, (FDT Matrix Technology®; Welch Allyn and Zeiss-Humphrey, Dublin, CA, USA), uses stimulus field formed by 5° squares with a spatial frequency of 0.50 cycles/degree and a temporal frequency of 18 Hz. The advantage offered by Matrix is that the default algorithm has been optimized to reduce the testing time and its higher spatial resolution allows the examination in similar locations tested by conventional perimetry.¹⁷ The first-generation FDT presents stimuli in a field formed by a

10° square, while the FDT Matrix presents it in a field formed by a 5° square. This higher spatial resolution means that the results from the new FDT tests are more topographically coordinated than the first-generation FDT using the same number of points as the conventional perimetry.

Multifocal visual evoked potential

The multifocal visual evoked potential (mfVEP) is a useful objective functional test in the assessment and diagnosis of glaucoma.¹⁸ The mfVEP fills an important gap in the functional assessment of glaucoma, allowing spatially localized damage to be identified with little or no active patient participation.

This study aims to evaluate the sensitivity and specificity of the FDT Matrix and mfVEP for detection of functional glaucoma defects in different groups—normal, glaucoma suspects, and patients with OAG, including those with pigment dispersion or pseudoexfoliation, and to compare the monocular and interocular mfVEP.

Methodology

Sample characterization and description of the tests

Ninety-five eyes of 23 normal subjects, 33 patients with suspected glaucoma, and 39 patients with OAG, including those with pigment dispersion or pseudoexfoliation, were enrolled in a cross-sectional study. Participants underwent a complete eye examination with measurement of visual acuity, applanation tonometry by Goldman's tonometer, dark room gonioscopy, and fundus biomicroscopy. The right eye of each patient was chosen for data analysis.

Standard automated perimetry

Visual field testing was performed with the Humphrey Field Analyzer® 850 (Carl Zeiss Meditec, Dublin, CA, USA). SITA Standard 24-2 strategy, with stimulus size Goldmann III, was used. Examinations were performed by the same examiner and interpreted by statistical package (STATPAC 2; Carl Zeiss Meditec). All patients had undergone at least two previous rounds of visual field testing. The examination would only be considered for analysis if present reliability indices were within normal limits – a loss of fixation index lower than 20% and rates of false-positive and false-negative less than 33%.¹⁹ Anderson's criteria of abnormalities (described elsewhere) was considered to evaluate the changes on visual fields.²⁰

Frequency doubling perimetry

FDT Matrix examinations were performed with the FDT Matrix Technology® (Welch Allyn and Zeiss-Humphrey), strategy 24-2 of the central area of the visual field, and

interpreted by the package for statistical analysis of the device itself. All patients underwent at least two previous examinations. Several authors suggest different interpretation criteria of the FDT.^{20–22} In this study we used the one suggested by Landers et al²³ considering a defect when two or more adjacent regions had $P < 5\%$, or an area with a defect with $P < 1\%$ on the pattern deviation plot.

The mean deviation (MD) and pattern standard deviation (PSD) global indices were considered for analysis. Like SAP, the examination would only be considered for analysis if present reliability indices were within normal limits – a loss of fixation index lower than 20% and rates of false-positive and false-negative less than 33%.

Multifocal visual evoked potential

The mfVEP testing was done with Veris software, Dart Board 60 with Pattern (Electro-Diagnostic Imaging, Redwood City, CA, USA). Each patient was prepared with the proper position of the electrodes as described above and the full test cycle containing four to eight measurements in each eye. An interval of 5 minutes between the first and second measurements of each eye was observed. The detailed mfVEP technique is described elsewhere.²⁴

A cluster was considered when two adjacent points were observed with $P < 1\%$ and three adjacent points with $P < 5\%$, and at least one of $P < 1\%$. We excluded points that cross the hemifield or affect the periphery of noncontinuous mode.²⁴

Recruitment

Recruitment of patients was done in 2006 through clinical evaluation of glaucoma in the New York Eye and Ear Infirmary (NYEEL), New York, NY, USA, under the supervision of Robert Ritch, Jeffrey Liebmann, and Celso Tello. Normal subjects were volunteers recruited from the staff of NYEEL and the healthy companions of patients.

Inclusion criteria

1. Normal: Individuals with IOP < 21 mmHg at two consecutive measurements on different days, normal RNFL; optic disc with cup/disc ratio of 0.5 or less balanced, without any signs of glaucomatous optic neuropathy; SAP within normal limits and no family history of glaucoma. This group was designated the “normal” group.
2. Patients with suspected glaucoma: Patients with suspicious changes in RNFL and/or optic disc, but SAP within normal limits. Ocular hypertensive patients were not included in this study. This group was designated the “suspect” group.

3. Patients with OAG, including those with pigment dispersion or pseudoexfoliation. The diagnosis of glaucoma in eyes without ocular hypotensive medication was made based on the values of IOP > 21 mmHg in addition to typical features of glaucomatous optic neuropathy and correspondent SAP defects. This group was designated the “glaucoma” group. In glaucoma patients using ocular hypotensive medication, IOP was not a criterion for inclusion or exclusion. In all glaucomatous eyes, the visual field loss on SAP was used to classify the severity of glaucoma as mild, moderate, or advanced, according to the criteria of Hodapp et al.²⁵

Exclusion criteria

Individuals under 18 years, with low visual field reliability index, visual acuity worse than 20/40, refractive error $> \pm 5$ diopters spherical and cylindrical to ± 3 diopters, pupillary diameter lower than 2 mm, history of corneal eye surgery, blunt trauma, cataract surgery less than 3 months from the beginning of the study, inability to return to established visits, ocular hypertension, Alzheimer's, Parkinson's, or other neurodegenerative disease were excluded.

Statistical analysis

Descriptive analysis of the sample

The intraclass correlation coefficient (ICC) confidence interval (CI) of 95% was applied to the MD and SAP PSD to identify the presence of dependence and correlation between the eyes.

The sensitivity/specificity of SAP, FDT, and interocular mfVEP ratio methods was evaluated using Receiver Operating Characteristics curves⁵¹ with respect to ophthalmic indicators (MD, PSD, noise, signal, and alpha). Specificity and sensitivity for each of these methods was also calculated. For the group variable, which has three categories, we adopted the nonparametric Kruskal–Wallis test,²⁶ which allows multiple comparison k, treatments, or categories. A significance level of 5% was considered in all statistical tests. Analyses were performed in SPSS software, version 13 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA.).

Ethics and good practice

The study was conducted in accordance with national and international resolutions, as described in the following documents: the Declaration of Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice – 1996, and Resolution 196/96 and 257/97 of the National Health

Council. The Ethics Committee at NYEEI previously approved this study. In addition, the survey was presented and approved by the Ethics Committee in Research of the Federal University of São Paulo.

Results

The SAP MD and SAP PSD ICC ranged between 0.284 to 0.832 (0.631 mean value) and -0.275 to 0.551 (0.167 mean value), respectively, showing the presence of interdependency between right and left eyes.

Descriptive analysis of the sample

The study sample comprised 95 eyes of 95 patients: 23 (24.2%) normals, 33 (34.7%) suspects, and 39 (41.1%) glaucomatous. Among the patients with glaucoma, four had pseudoexfoliation (10%) and one had pigmentary glaucoma (2.5%). Twenty-five eyes (64.1%) from the glaucoma group were classified as mild, five (12.8%) as moderate, and nine (23.1%) as advanced. Forty-three patients were females and 52 were males. The highest mean age belonged to the glaucoma group (66.3 years) and the lower mean age belonged to the normal group (53.7 years) ($P=0.006$).

Regarding visual acuity, 86.96% of normal patients and 84.85% of glaucoma suspects had acuity 1.0, while 51.28% of the glaucoma patients were in this group.

IOP (mean ± standard deviation) was 14.61±2.92 mmHg in the normal group, 16.89±3.74 mmHg in the suspect group, and 18.82±3.40 mmHg in the glaucoma group ($P<0.0001$) (Table 1).

Sensitivity and specificity

The FDT Matrix had a sensitivity–specificity of 92.3%–80% and 84.6%–80% in relation to MD and PSD, respectively (Tables 2 and 3). On the other hand, interocular mfVEP had a sensitivity of 64.9% and a specificity of 69.6% (Table 4).

Receiver Operating Characteristics curves

The FDT Matrix showed an area under the curve (AUC) of 0.756 (95% CI, 0.640–0.849) and 0.761 (95% CI, 0.645–0.854) in relation to MD and PSD, respectively (Figure 1). On the other hand, the interocular mfVEP demonstrated

Table 2 Sensitivity and specificity of MD FDT among groups

MD FDT	Normal		Suspect		Glaucoma	
	n	%	n	%	n	%
Normal	16	80	21	63.6	3	7.7
Abnormal	4	20	12	36.4	36	92.3

Abbreviations: FDT, frequency-doubling perimetry; MD, mean deviation.

an AUC of 0.564 (95% CI, 0.442–0.681) and AUC 0.512 (95% CI, 0.392–0.632) in relation to signal and alpha index, respectively (Figure 2). The monocular mfVEP demonstrated an AUC of 0.568 (95% CI, 0.446–0.684) and AUC 0.538 (95% CI, 0.417–0.657) in relation to signal and alpha index, respectively (Figure 3). The comparisons of these values are demonstrated in Figure 4.

Discussion

The aim of this study was not to identify the correlation between SAP and FDT Matrix, but between the FDT Matrix and mfVEP. Nevertheless, it is noteworthy that the SAP and FDT tests correlate. Quigley²⁷ demonstrated a good correlation between sensitivity and specificity indices of the FDT and Humphrey Field Analyzer[®] 850 (Carl Zeiss Meditec). Sponsel et al²¹ also identified a good correlation between the FDT and Humphrey Field Analyzer[®] 850 (Carl Zeiss Meditec) 30-2 in 42 glaucoma patients and 14 normal subjects. On the other hand, Kondo et al²⁸ failed to show an acceptable correlation between the values of the FDT with Humphrey in eleven patients with normal tension glaucoma.

Compared to FDT, results of preliminary studies showed a high sensitivity in both screenings to differentiate healthy individuals from those with glaucoma and to quantify glaucomatous damage.^{20,27} When used for screening, Samuels and Johnson¹⁶ reported that FDT has a good sensitivity and specificity (Sensitivity 73% and specificity 93%). In our study, FDT MD showed a sensitivity of 92.3% and specificity of 80% to differentiate normal and glaucomatous eyes.

One of the objectives of this study is the identification of the best FDT criteria of abnormality. Considering the criteria suggested by Landers et al²⁹ and Fogagnolo et al²² we compared different criteria for abnormality for screening glaucoma patients, using the FDT, and identified the criterion of at least one point with $P<5%$ as the most suitable, with

Table 3 Sensitivity and specificity of PSD FDT among groups

PSD FDT	Normal		Suspect		Glaucoma	
	n	%	n	%	n	%
Normal	16	80	22	66.7	6	15.4
Abnormal	4	20	11	33.3	33	84.6

Abbreviations: FDT, frequency-doubling perimetry; PSD, pattern standard deviation.

Table 1 Demographics

Gender	Male	54.7%
	Female	45.2%
Age	Glaucoma	66.3 years
	Suspect	60.6 years
	Normal	53.7 years
Visual acuity 1.0	Glaucoma	51.28%
	Suspect	84.85%
	Normal	86.96%

Table 4 Sensitivity and specificity of interocular mfVEP among groups

mfVEP interocular	Normal		Suspect		Glaucoma	
	n	%	n	%	n	%
Normal	16	69.6	21	63.6	3	7.7
Abnormal	7	30.4	12	36.4	36	92.3

Abbreviation: mfVEP, multifocal visual evoked potential.

AUCs of 0.8875 (S.87.5% and E.90%). In another study,³⁰ 14% of ocular hypertensive patients had abnormal FDT with a specificity of 96%. The authors considered the criterion of two or more points with $P < 0.05$ in the pattern deviation plot (E.96%). Fogagnolo et al²² reported an AUC of 0.926 using the FDT for glaucoma screening, very close to the values found in this study, where AUC was 0.922 between normal and glaucomatous patients and 0.721 between normal and glaucoma suspects.

In our study, the FDT Matrix showed an AUC of 0.756 (95% CI, 0.640–0.849) and 0.761 (95% CI, 0.645–0.854) compared to the MD and PSD, respectively. Depending on the criteria used, Ferreras et al³¹ found similar values, with AUC ranging from 0.703 to 0.861.

The mfVEP is an objective method of functional assessment with potential use in glaucoma.³² Unfortunately, it shows a significant variability between patients, mostly due to anatomical differences in the visual cortex, such as the location of the calcarine cortex compared to the position of the external electrodes, and differences of cortical folds.³³ One way to reduce this individual variability was the

perception that the mfVEP responses of the two eyes from the same individual are virtually identical. In glaucoma patients with asymmetric visual field loss, the comparison between the eyes (interocular) is able to identify this difference.^{34,35} This diagnostic ability is lost when faced with symmetric functional losses. In such cases, monocular analysis is recommended, which is compared with the database of normal patients.^{36–38}

Studies have shown that functional tests like FDT and short-wavelength automated perimetry can detect defects in 28% to 39% of suspect glaucoma eyes with normal SAP.^{39,40} The authors found a similar result with mfVEP where 20% of glaucoma suspect patients showed an abnormality not found in standard SAP. In our study, 30.4% of normal patients showed an abnormal interocular mfVEP and 35.1% of glaucoma patients showed normal interocular mfVEP.

Graham et al⁴¹ using a different analysis of the mfVEP criteria, reported a rate of 18.4% change in their glaucoma suspects with normal SAP; 18.2% of glaucoma suspects had abnormal values of interocular mfVEP. Their study suggested a potential use of the mfVEP in patients with suspect glaucoma and normal SAP, suggesting an early functional diagnosis. Nevertheless, in our study, both the interocular and monocular evaluation showed poor ability to differentiate suspect to glaucomatous eyes, with AUC 0.502 and 0.532, respectively.

In disagreement with Hood et al¹⁷ who reported a greater ability to identify the interocular mfVEP glaucomatous

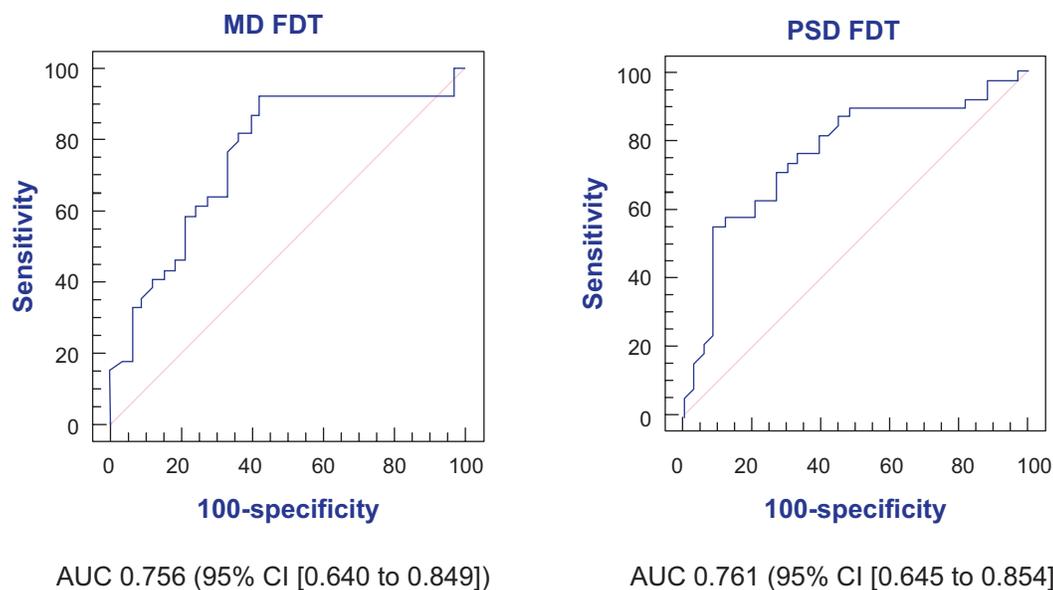


Figure 1 AUC of MD and PSD from FDT Matrix.

Abbreviations: AUC, area under the curve; CI, confidence interval; FDT, frequency-doubling perimetry; MD, mean deviation; PSD, pattern standard deviation.

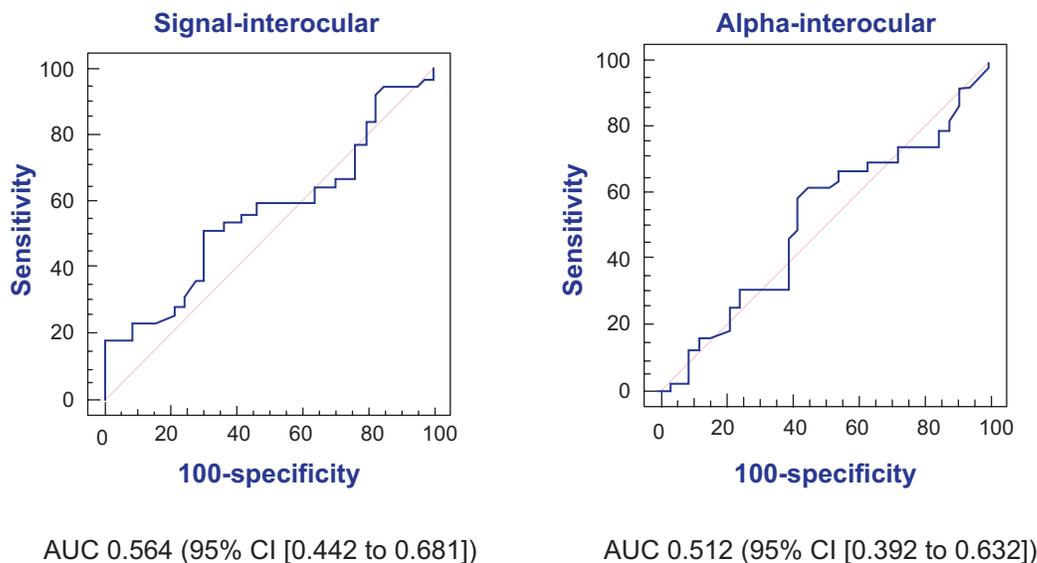


Figure 2 AUC of signal and alpha from interocular mfVEP.

Abbreviations: AUC, area under the curve; CI, confidence interval; mfVEP, multifocal visual evoked potential.

damage in relation to monocular mfVEP, our result showed no significant difference between the monocular and interocular mfVEP values with AUC of 0.564 versus 0.568 ($P=0.326$).

One limitation of this study was the use of SAP as inclusion criteria and in distribution of eyes among the normal, suspect, and glaucoma groups. Its use was motivated by the possibility to compare two different functional techniques, the FDT and mfVEP, which possibly stimulate distinct cell subsets.^{42,43} Another limitation was the difference in age groups of individuals. The glaucoma group skewed older. It is known that the incidence of glaucoma increases with advancing years. With increasing age, a nonlinear decrease

in the sensitivity of retinal ganglion cells occurs in both the SAP⁴⁴ as well as the FDT.⁴⁵

In conclusion, our results confirm the superiority of FDT Matrix to mfVEP in the detection of glaucomatous defects. We could not confirm the efficacy of mfVEP in detecting early glaucomatous defects, and found no difference in AUC between the interocular and monocular mfVEP analysis.

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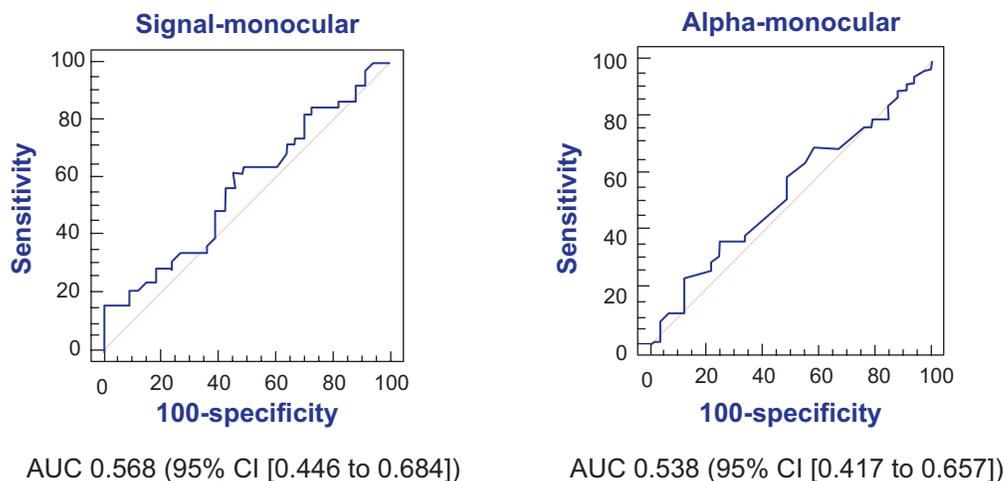


Figure 3 AUC of signal and alpha from monocular mfVEP.

Abbreviations: AUC, area under the curve; CI, confidence interval; mfVEP, multifocal visual evoked potential.

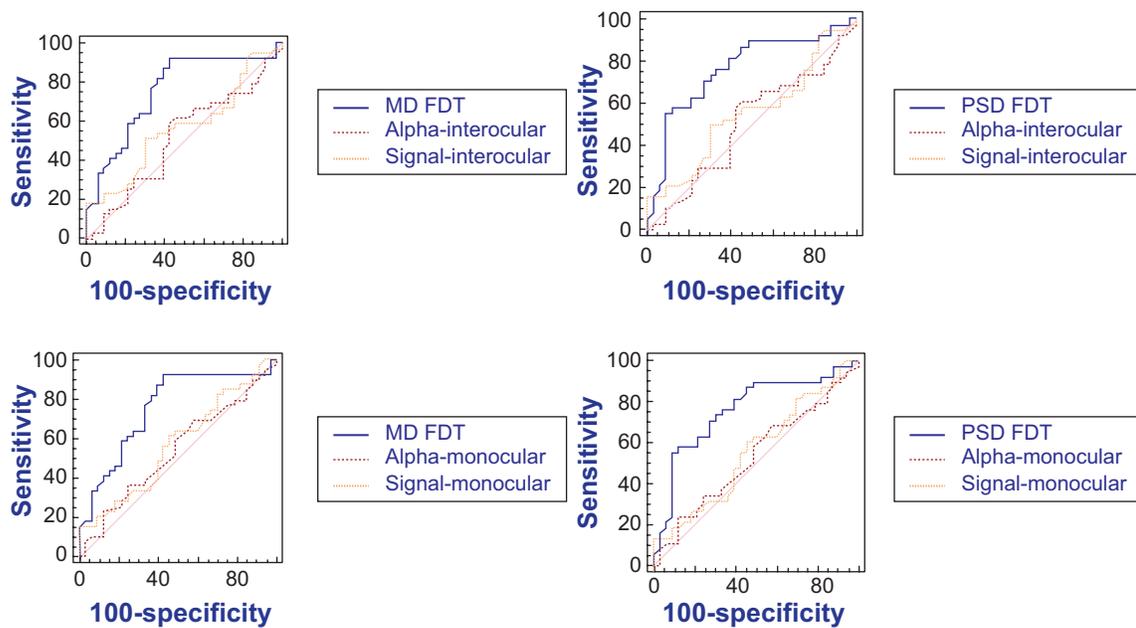


Figure 4 Comparison of the AUCs between FDT Matrix and mfVEP.

Note: $P < 0.05$.

Abbreviations: AUC, area under the curve; FDT, frequency-doubling perimetry; MD, mean deviation; mfVEP, multifocal visual evoked potential; PSD, pattern standard deviation.

Disclosure

The authors declare no conflicts of interest in this work.

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