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Nomograms for Converting Perimetric Sensitivity From Full Threshold and SITA Fast to SITA Standard in Patients With Glaucoma and Healthy Subjects

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Purpose: The purpose of this study was to develop nomograms for converting Full Threshold (FT) and Swedish Interactive Threshold Algorithm (SITA) Fast (SF) tests to SITA Standard (SS) tests with the Humphrey Field Analyzer in patients with glaucoma and healthy subjects.

Methods: One eye each of 49 patients with glaucoma and 50 healthy subjects was tested in 4 and 2 sessions (each containing the 3 strategies), respectively, over 4 weeks. The difference between pointwise Best Available Estimate (BAE; mean of all FT tests) and SS sensitivity at each session was used to derive four nomograms. Nomogram accuracy was assessed by: (1) comparing the converted FT to actual SS sensitivity (omitting the test session used to derive the nomogram) and (2) comparing the distribution of the differences between the converted and actual SS sensitivity to the actual SS test-retest differences. The process was repeated for SF and healthy subjects.

Results: In patients with glaucoma, 39.85% and 59.69% of the conversion differences from FT were within 1 dB and 2 dB of the mean, respectively. The respective figures for SF were 45.69% and 65.04%, and in healthy subjects, they were 54.34% and 76.48% for FT and 61.17% and 82.66% for SF. The difference in the mean conversion and test-retest differences was $<$0.5 dB for all comparisons, with an overlap in distributions ranging from 78.75% to 85.24. There was no association between conversion differences and BAE for either FT or SF in either subject group.

Conclusions: Nomograms to convert FT and SF tests to SS tests yield accuracies that are negligibly different from test-retest differences with SS.

Translational Relevance: Nomograms allow direct comparisons between different perimetric strategies for a more comprehensive assessment of visual field change.

Introduction

Progress in thresholding algorithms in perimetry led to the transition from staircase strategies,[1,2] such as the Full Threshold (FT) algorithm on Humphrey Field Analyzer (HFA; Zeiss Humphrey Systems, Dublin, CA) introduced in the 1980s, to the quicker maximum likelihood strategies, such as the Swedish Interactive Threshold Algorithms (SITA Standard [SS] and SITA Fast [SF]) at the beginning of the 1990s.[3]

Both for healthy subjects and patients with glaucoma, the test time for SS is approximately 50% less compared to FT, whereas that for SF is around 70% compared to FT.[4–7] It has been hypothesized that the decrease in test time and the consequent reduction in fatigue results in the higher sensitivity obtained with SS and SF.[8,9] Additionally, visual field defects

in patients with glaucoma with SS and SF appear more statistically significant compared to FT, whereas normal subjects have fewer statistically depressed test locations with SS compared to FT and SF.[9]

These large differences between thresholding strategies has led to the recommendation that tests with a mixture of strategies should be cautiously compared and that new baselines should be obtained when switching from FT to the SITA strategies for follow-up.[10–12] However, a negative consequence of this approach is loss of a potentially large amount of data obtained before the change, impacting both longitudinal research studies that began testing with FT and the clinical follow-up of patients with glaucoma tested with multiple strategies over time. Given that in most patients with glaucoma, the rate of progression is slow,[13,14] a higher number of examinations is required to detect statistically meaningful change.[15,16] In many circumstances, depending on the age of the patient and severity of visual field loss, reliable detection of the rate of visual field change can be very important for guiding therapeutic interventions and follow-up strategies for avoiding visual disability.[15]

Therefore, there is a need for usable methodology that allows conversion of visual field results, in this case, FT and SF into SS. However, it is not possible to use a global linear conversion between the tests because the differences among the three strategies vary along the dynamic range.[17] The objective of this study was to create nomograms for the pointwise conversion of the thresholds obtained from FT and SF to SS in patients with glaucoma and healthy subjects.

Methods

Subjects

We analyzed visual field data from 49 patients with glaucoma[17] and 50 healthy subjects. All subjects were recruited from the Tajimi Municipal Hospital (Tajimi, Japan). Ethics approval was obtained from the ethics committee of the Tajimi Municipal Hospital and each subject gave informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Patients with a clinical diagnosis of glaucoma were consecutively recruited. They were included into the study if they had best corrected visual acuity ≥20/20, optic disc damage, and/or retinal nerve fiber layer defects compatible with glaucoma and visual field damage. Glaucomatous visual field damage was defined by the Glaucoma Hemifield Test outside normal limits and hemifield abnormality according to Anderson Cluster Analysis (at least 3 contiguous non-edge depressed points to the 5% probability level, with at least one non-edge point depressed to the 1% level, not crossing the horizontal midline, in the pattern deviation probability plot).[18]

Healthy subjects were included if they had visual acuity ≥20/20, normal clinical eye examination, normal visual field, and no family history of glaucoma.

Subjects from both groups were excluded if they had refractive error exceeding 3 diopters (D) sphere or 3 D astigmatism, a history of systemic and ocular disease potentially affecting the visual field, eye trauma, or surgery.

Testing

Patients with glaucoma underwent 4 test sessions, with 1 week between sessions, whereas healthy subjects underwent 2 test sessions over approximately the same time period as the patients. Each session consisted of a 30-2 visual field examination (HFA, model 740; Zeiss Meditec, Dublin, CA, USA), for each strategy (FT, SF, and SS) performed in random order for each subject. Only one randomly selected eye per subject was tested and only reliable visual fields (false-positive and false-negative errors <15% and fixation losses <20%) were selected. For statistical analysis, all visual fields were converted to right-eye format. The foveal and two blind spot test locations were excluded from the analysis.

Best Available Estimate and Nomograms

For the glaucoma group, the mean of the pointwise sensitivities, obtained with the FT strategy of each session, was used to determine the Best Available Estimate (BAE). We used this approach (as opposed to the results of a single test) because of possible outlier effects of single tests. The BAE was compared to the median of the respective pointwise sensitivity of each SS session in order to derive four nomograms for the FT to SS conversion (one per session, Fig. 1A). The same method was used to compute the BAE of the sensitivities obtained with SF and to derive the four nomograms for the SF to SS conversion. The analysis for the healthy group was performed separately with the same methodology applied to the two available test sessions (Fig. 1B).

Because of higher variability at lower sensitivity[17,19–21] and the lower number of observations at these sensitivities, cut offs were applied at 10 dB in the glaucoma group and 20 dB in the healthy group (see Supplementary Fig. S1). Data below these cut offs were excluded from the analysis.

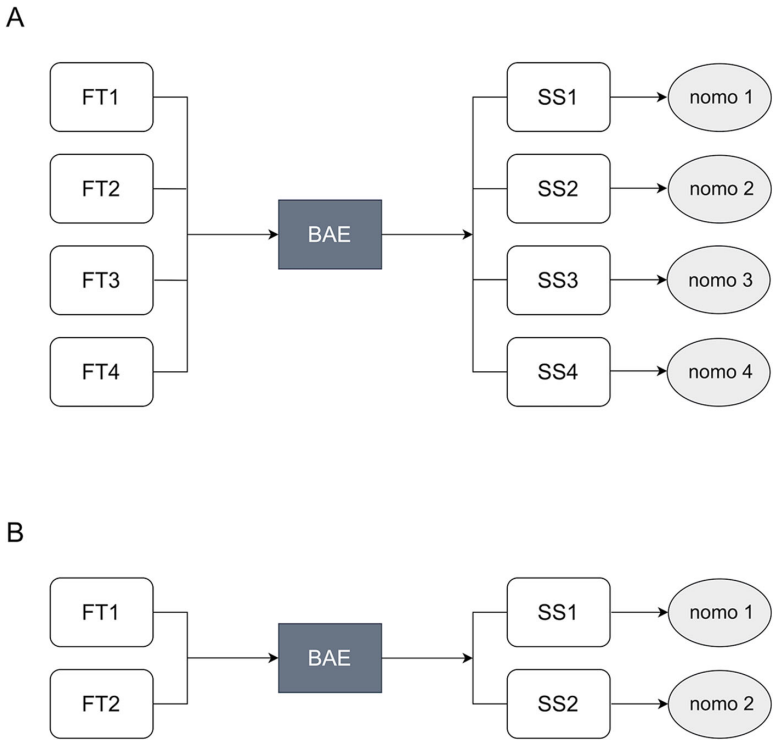

Figure 1. Nomograms obtained from comparing the Best Available Estimate of pointwise sensitivity with Full Threshold to each with SITA Standard test in the glaucoma (**A**) and healthy (**B**) groups. The same methodology was used for the SITA Fast nomograms. FT = Full Threshold; BAE = Best Available Estimate; SS = SITA Standard; nomo = nomogram.

Derived Single Nomograms

To provide a single nomogram for the FT and SF conversions to SS in the glaucoma group, we derived the mean of the four nomograms previously obtained for each strategy. We used these two derived single nomograms to convert sensitivities of each visual field test point and obtain SS conversions, from FT and SF, respectively. However, to avoid a biased estimate, for each session of each strategy, we excluded the nomogram obtained from the BAE derived from the same session to be converted. In other words, we used a partial mean (i.e. the average of 3 of the 4 available original nomograms). For example, the mean of nomograms 2, 3, and 4 was used to convert pointwise values in the FT1 session (Fig. 2A).

In the healthy group, because only two sessions were available, the two original nomograms were used in alternative order both for FT and SF (e.g. nomogram 1 for FT2 and nomogram 2 for FT1; Fig. 2B).

Evaluation of Single Nomograms: Conversions Differences and Test-Retest Differences

To quantify the performance of the single nomograms and the validity of the conversions, we compared the differences between the converted SS values from both FT and SF sensitivities to the actual SS sensitivities. In addition, we compared the pointwise differences between converted SS sessions to corresponding pointwise test-retest differences between actual SS sessions.

To achieve this, we first compared, in a pointwise manner, each converted sensitivity with the corresponding actual SS value in the same session (e.g. the converted SS1 was compared to the actual SS1; see Fig. 2). Then, the actual SS sessions were compared consecutively with each other to estimate the pointwise test-retest differences in order to obtain the same number of converted and test-retest differences (for each strategy, 4 SS test-retest differences sets for the glaucoma group and 2 for the healthy group; Fig. 3). Only SS test points corresponding to those previously used to compute converted SS and conversions differences, respectively, for FT and SF, were used to obtain SS test-retest differences.

Statistical Analysis

Demographic characteristics of the glaucoma group and the healthy group were compared with the *t*-test or Mann-Whitney test, depending in the distribution of the continuous variables, and with the χ^2 test, for

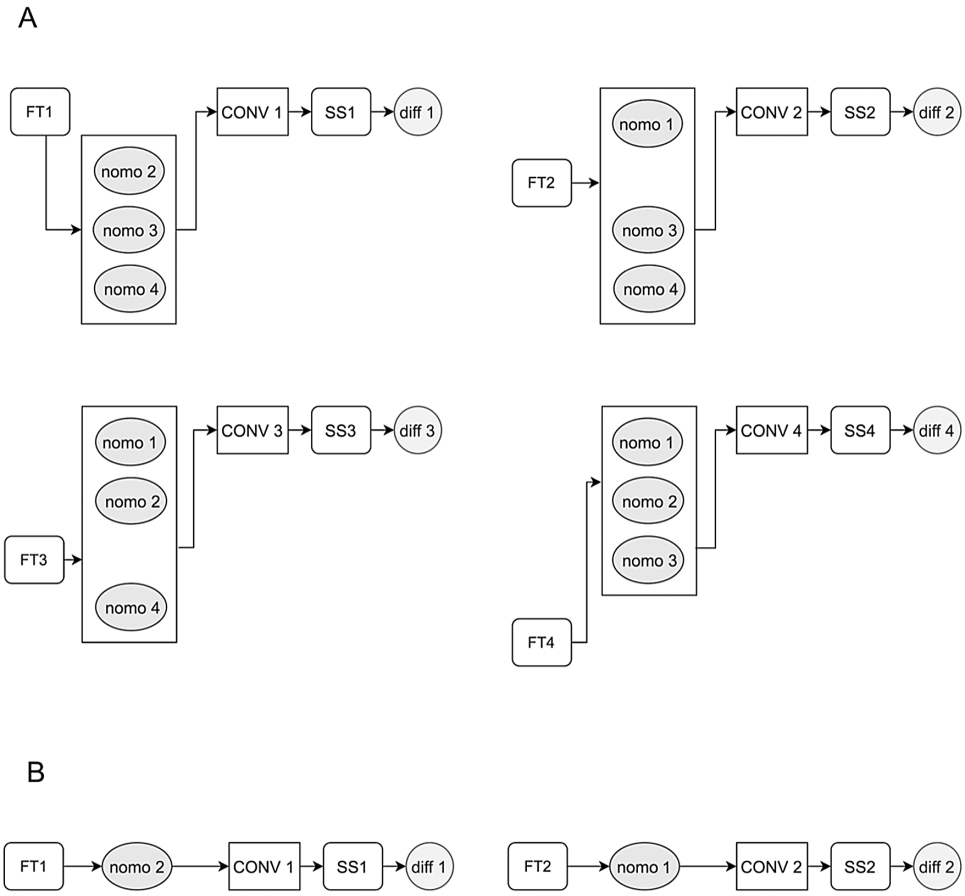

Figure 2. Conversion of Full Threshold sessions by using the partial mean of the nomograms. The converted values were compared to the actual SS threshold to compute the conversion difference for each of the four possible combinations for the glaucoma group (**A**) and the two possible combinations for the healthy group (**B**). The same methodology was used for SITA Fast sessions. FT = Full Threshold; nomo = nomogram; CONV = converted value; SS = SITA Standard; diff = conversion difference.

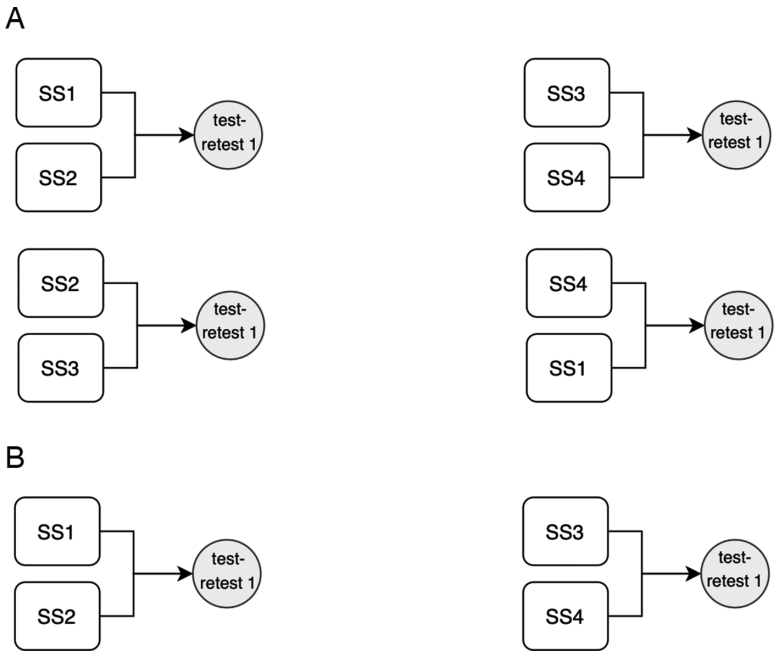

Figure 3. SITA Standard test-retest differences for the glaucoma (**A**) and healthy (**B**) groups. SS = SITA Standard.

categorical variables. The Wilcoxon test was used to verify differences in mean sensitivity obtained with FT, SF, and SS for each patient in both subject groups. Conversions and SS test-retest differences for each strategy in each group were compared by computing the overlapped estimated area of each respective paired probability density distribution, expressed as percentage.[22] The relationship between conversion differences and BAE was assessed with Pearson's correlation coefficient. Statistical significance was assumed when $P < 0.05$. We used open-source software (version 3.6.0, R Core Team, 2019; R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) and R Studio (RStudio Team, 2020; RStudio: Integrated Development for R. RStudio, PBC, Boston, MA; URL http://www.rstudio.com/) to conduct statistical analysis. Overlapped estimate area was computed using overlapping package (version 1.6).[23]

Results

The mean unweighted mean deviation derived from the first SS session was −5.92 dB (range = +2.81 dB to −20.18 dB) for patients with glaucoma and +1.31 dB (range = +3.56 dB to −1.44 dB) for healthy subjects. Patients with glaucoma were older than healthy subjects (median age 63 vs. 46.5 years, $P < 0.01$). There was a statistically significant difference in sex distribution in the glaucoma group in which the percentage of female subjects was higher than male subjects (77.5% vs. 22.5%; $P < 0.01$) compared with healthy group, in which there was no statistically difference in sex distribution (58% female subjects vs. 42% male subjects, $P = 0.25$).

The mean sensitivities obtained by FT, SF, and SS during test sessions are shown in Figure 4. The healthy group had higher mean sensitivity in all sessions compared with the glaucoma group. Among the strategies, SF yielded the highest sensitivity whereas FT yielded the lowest in each session in both subject groups. On average, differences in sensitivity estimates among strategies were smaller in the healthy group: SF yielded estimates 0.49 dB higher than SS ($P < 0.01$), and SS yielded estimates 0.84 dB higher than FT ($P < 0.01$), compared with the glaucoma group in which SF provided estimates 0.79 dB higher than SS ($P < 0.01$) and SS provided estimates 0.94 dB higher than FT ($P < 0.01$).

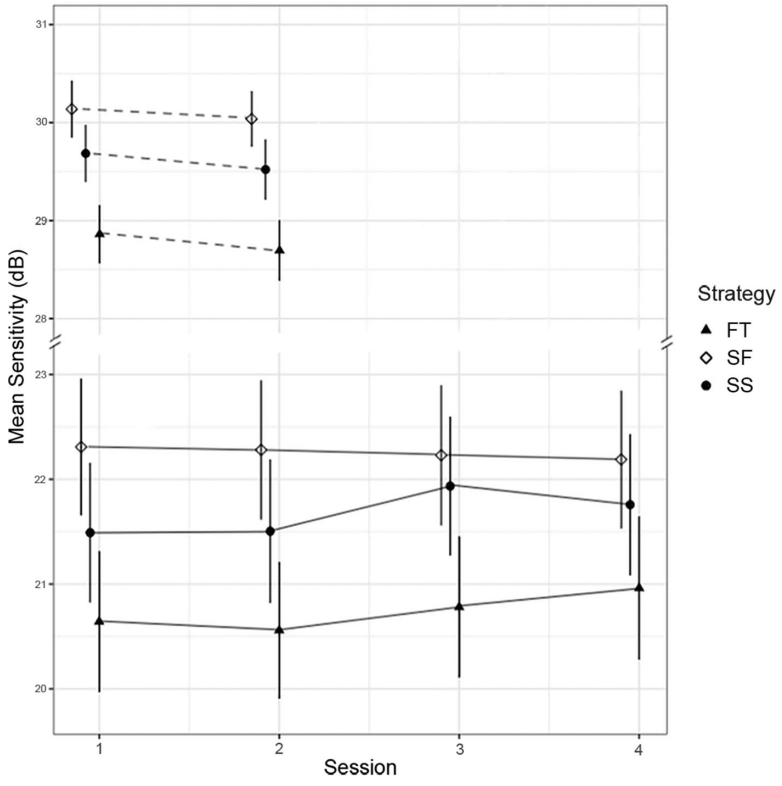

Figure 4. Mean Sensitivity of each test strategy for each session for the glaucoma group (*solid lines*) and healthy group (*dashed lines*). Error bars show standard error of the mean. FT = Full Threshold; SF = SITA Fast; SS = SITA Standard.

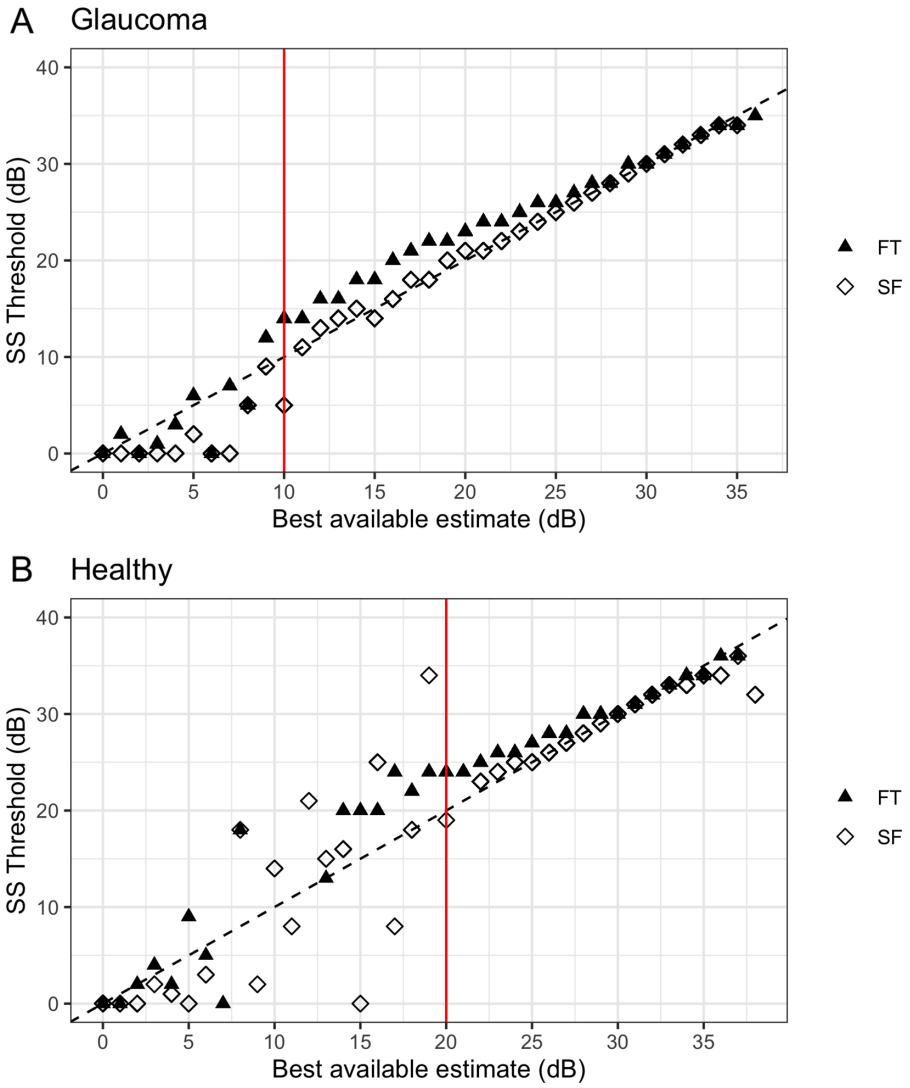

Figure 5. Single nomograms for Full Threshold and SITA Fast strategies for the glaucoma (**A**) and healthy (**B**) groups. The *red lines* indicate the cut off values above which the analysis was conducted. FT = Full Threshold; SF = SITA Fast; SS = SITA Standard.

The nomograms for the conversion of FT and SF to SS for the glaucoma and healthy groups are shown in Figure 5 and in tabular format in Supplementary Table S1. At higher sensitivity (>30 dB) in both subject groups, there was a close correspondence between FT and SS and the conversion factor to be applied ranged from 0 to −1 dB. Below 30 dB, the factor was instead positive, between +1 dB and +4 dB in the glaucoma group and +1 dB and +3 dB in the healthy group, as sensitivity decreased. The correspondence between SF and SS was higher than that compared with FT in both subject groups, particularly above 25 dB. Between 25 dB and the cut off value below, which data were not analyzed (red lines, Fig. 4), the conversion factor ranged from +1 to −1 dB.

Figure 6 shows the distributions of FT and SF conversion differences and SS test-retest differences for the glaucoma group, whereas Figure 7 shows the corresponding data for the healthy group. In the glaucoma group, 39.85% of the conversion differences for FT and 45.69% of the conversion differences for SF were within 1 dB of the mean, whereas 59.69% and 65.04%, respectively, were within 2 dB of the mean (Figs. 6A, 6B). In the healthy group, the corresponding values were higher: 54.34% and 61.17%, respectively, within 1 dB of the mean and 76.48% and 82.66%, respectively, within 2 dB of the mean (see Figs. 7A, 7B). As a comparison with the test-retest data, in the glaucoma group, 46.92% of SS test-retest differences for FT and 45.07% of SS test-retest differences for SF were within 1 dB of the mean, whereas 66.77% and 64.31%, respectively,

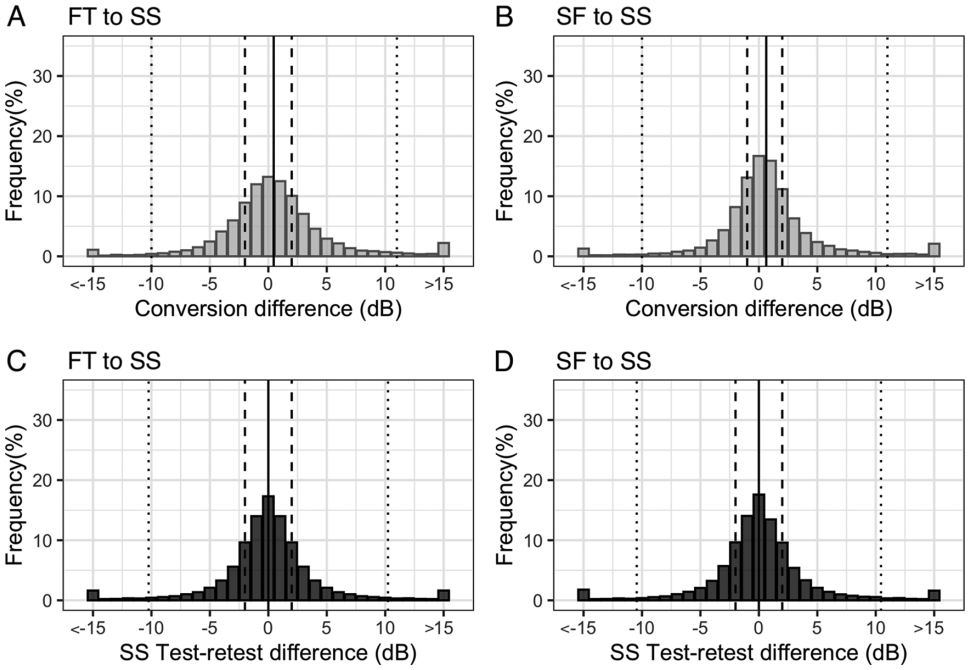

Figure 6. Conversion difference distributions for Full Threshold (**A**) and SITA Fast (**B**) the glaucoma group. Distribution of SITA Standard test-retest differences at the corresponding test points (**C** and **D**) shown in **A** and **B**. Median (*solid lines*), first and third quartiles (*dashed lines*) and 2.5th and 97.5th percentiles (*dotted lines*) are displayed. FT = Full Threshold; SF = SITA Fast; SS = SITA Standard.

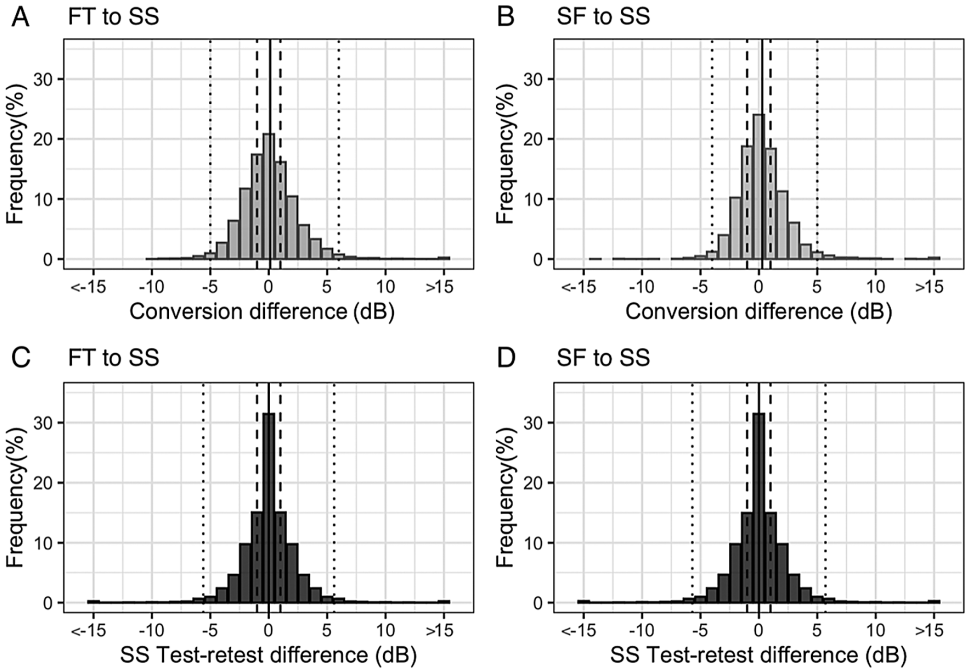

Figure 7. Conversion difference distributions for Full Threshold (**A**) and SITA Fast (**B**) the healthy group. Distribution of SITA Standard test-retest differences at the corresponding test points (**C** and **D**) shown in **A** and **B**. Median (*solid lines*), first and third quartiles (*dashed lines*) and 2.5th and 97.5th percentiles (*dotted lines*) are displayed. FT = Full Threshold; SF = SITA Fast; SS = SITA Standard.

were within 2 dB (Figs. 6C, 6D). In the healthy group, 61.52% of SS test-retest differences for FT and 61.35% of SS test-retest differences for SF were within 1 dB, whereas 80.98% and 80.89%, respectively, were within 2 dB (Figs. 7C, 7D).

Comparison between conversion differences and SS test-retest differences distributions are reported in the Table. The means of the distributions of conversion differences for FT and SF were slightly higher than those of the SS test-retest differences in both subject

Table. Conversion Difference and SS Test-Retest Difference Distributions

	FT		SF	
	Conversion Difference	Test-Retest Difference	Conversion Difference	Test-Retest Difference
Glaucoma group				
Mean (SD), dB	0.46 (5.09)	0 (4.88)	0.63 (5.25)	0 (5.16)
Overlap	85.24%		84.07%	
Healthy group				
Mean (SD), dB	0.12 (2.60)	0 (2.80)	0.29 (2.38)	0 (2.85)
Overlap	78.75%		78.39%	

FT = Full Threshold; SF = SITA Fast; SD = standard deviation.

groups. However, in the glaucoma group, FT and SF conversion difference distributions highly overlapped with the SS test-retest difference distributions (85.24% and 84.07%, respectively, for FT and SF, with very similar percentile values; see Fig. 6), whereas the percentages for the healthy group were slightly lower (78.75% and 78.39%, respectively, for FT and SF). Furthermore, in both subject groups, the FT to SS conversion difference distribution had a higher overlap with the SS test-retest differences compared to the SF to SS conversion difference.

There was no association between conversion differences and BAE values for either FT or SF in either subject group (Fig. 8).

Discussion

Differences in thresholding strategies in automated perimetry make it challenging to evaluate results in patients who have been followed for an extended period with a combination of test strategies. Humphrey perimeters come with built-in software (Glaucoma Progression Analysis [GPA]) that allows the analysis of serial visual field examinations to help identify progression, even with a mix of examinations with different strategies. However, the possible combinations of strategies are limited to FT-SS and FT-SF in the HFA-II and to SF-SS in the HFA-III, which no longer includes FT, but the new SITA Faster strategy.[24,25] Moreover, whereas for follow-up tests the GPA provides arithmetic differences in pattern deviation from baseline, no account is made for the fact that these values may be derived from different test strategies. Considering these limitations, in patients switching from FT to SS, analysis of data collected prior to the introduction of SS could provide a better understanding of progression with long-term follow-up if a conversion strategy were available. Such an approach would also be useful in patients who have more recently switched from SS to SF. In this study, we used visual field data from patients with glaucoma and healthy subjects to create nomograms for converting FT and SF to SS, which is currently the most commonly used strategy with the HFA. To the best of our knowledge, there are no such published nomograms that allow this conversion in a pointwise manner with the aim of utilizing all tests and enhance the accurate detection of progression.

The results of our study show that the nomograms we proposed yield conversion values that are accurate. We found a similarity in the distributions of conversion differences and SS test-retest differences in both patients with glaucoma and healthy subjects, indicating that the error in conversion was comparable to the difference between a pair of SS tests (see Figs. 6, 7). There was, however, a higher percentage of overlap between FT and SS conversion differences in patients with glaucoma compared to healthy subjects (85.24% and 84.97%, compared to 78.75% and 78.39%, respectively). The fact that the patients with glaucoma had more test sessions compared to the healthy subjects, and consequently a higher number of observations available for the analysis, could have yielded a more precise conversion and higher overlap percentages between conversion differences and SS test-retest differences distribution.

Between 20 and 10 dB, the test-retest variability progressively increases.[17,21] In our sample, the number of observations in the 10 to 20 dB range allowed us to obtain reliable estimates of BAE and conversion factors within this range. As a consequence, this also allowed us to extend the range of the nomograms for patients with glaucoma. However, for values below 10 dB in the glaucoma group, where the limits approach the lower end of the dynamic range of the instrument, the high test-retest variability and the concomitant lower number of test points in our sample makes conversion likely to be imprecise, and we do

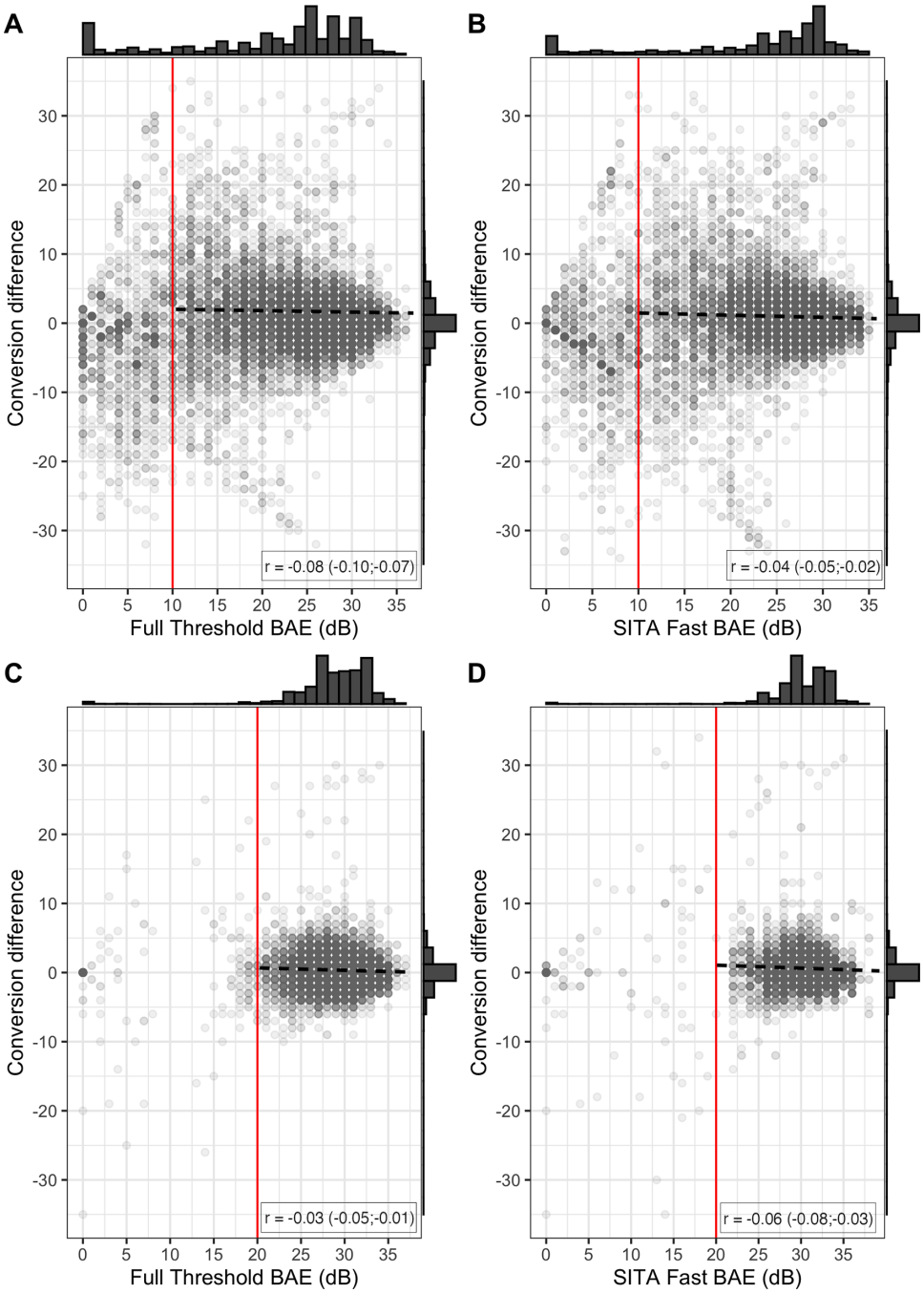

Figure 8. Scatterplot and marginal histogram illustrating conversion difference distributions as a function of Full Threshold and SITA Fast Best Available Estimate (**A** and **B**, respectively) in the glaucoma and healthy (**C** and **D**, respectively) groups. The *red lines* indicate the cut off values above which the analysis was conducted. The *dashed lines* represent the lines of best fit. The correlation coefficients with 95% confidence intervals are shown. BAE = Best Available Estimate.

not recommend use of the nomogram. Applying a conversion factor below the 10 dB cut off would increase conversion differences and further undermine the opportunity to compare tests and detect progression in these points. On the other hand, applying a cut off of 20 dB in healthy subjects would not have a practical impact, given that normal pointwise sensitivity is rarely lower than 20 dB.[26] In our healthy group, less than 2% of test points with SF and less than 3% of test points with FT had sensitivity less than 20 dB (see Supplementary Fig. S1). Therefore, because of the paucity of available data, a conversion of sensitivity below 20 dB in healthy subjects is also not recommended.

Nomograms are derived on the BAE of the sensitivity value for FT and SF. The sensitivity of a single test may not represent the true or "best" estimate of retinal sensitivity because of the test-retest variability of the instrument. However, the goal of our nomograms is not to address test-retest variability but to provide sensitivity conversions from FT and SF to SS, while remaining within the test-retest variability of SS itself. Therefore, the BAE could be considered as a surrogate for a single test.

A limitation of our method is that our nomograms assume an independent pointwise conversion from FT and SF to SS. Compared to FT, which uses a 4-2 dB stepwise algorithm at each test point,[1] SITA strategies use a Bayesian method with age-corrected normal sensitivity values, probability density function, dynamic monitoring of patient response times, and postprocessing adjustment of the final estimated sensitivity based on the values in adjacent test point locations.[3,27] In other words, the final sensitivity of one test point in the SITA strategies is not a simple pointwise estimate. Nonetheless, despite this limitation, our nomograms were still able to provide conversion differences that fall within the magnitude of test-retest differences of actual SS tests.

In addition to the probability-based algorithm, SF proceeds in 4 dB steps with one reversal, at all but 4 primary points (at 12.7 degrees from the fixation point, in each quadrant) where the classic 4-2 dB steps size is used. The stimulus sequence terminates when at least one positive response is recorded, ending the test sequence at that point. On the contrary, SS uses a 4-2 dB step size with 2 reversals for all points to determine sensitivity. As a result, compared to SS, SF has a predetermined lower level of precision in sensitivity estimate, but reduced test time.[5,6,28] The postprocessing and the predetermined level of precision of the SITA algorithms also explains the difference in sensitivity estimates among FT, SF, and SS. Our study confirms previous reports[8,29] of a difference in mean sensitivity of almost 1 dB between SS and FT tests and about 0.50 dB between SF and SS tests, in both subject groups (see Fig. 4).

We decided to conduct the analysis separately for patients with glaucoma and healthy subjects and to make separate pairs of nomograms in order to obtain the most accurate conversions possible for each sensitivity level. However, the differences between the nomograms of the 2 subject groups did not exceed 2 dB in the range of overlapping sensitivity values (between 21 and 35 dB; see Supplementary Table S1). Our study did not contain glaucoma suspects, however, given the minor differences between nomograms of patients with glaucoma and healthy subjects, either one could be used for this group of subjects.

Whereas FT nomogram may be more useful for research applications in the analysis of previously collected data, the SF nomogram may be more for useful in clinical applications. With the advent of the SITA algorithms, which reduce test times and yield comparative results to FT,[27,30,31] the latter is less attractive in clinical practice. Nevertheless, in cases where a large amount of FT data was collected prior to switching to SITA, there could be opportunities for effectively increasing the follow-up time in order to study the evolution of glaucomatous perimetric damage with SS without loss of data. In clinical practice, SF has become commonly used as an alternative to SS. In addition, although our study did not specifically address precision of threshold estimates with the different strategies, there is some evidence that SF is more precise than SS at higher sensitivities[17,32] and this evidence may support the use of SF in patients with very early damage. However, as the damage becomes more advanced, there is a need to estimate sensitivity with increasing precision and to better characterize visual field defect with SS. Therefore, it is possible that the two SITA strategies could be used over the course of the disease, for which the nomogram may have value.

In summary, we developed and tested the utility of nomograms that convert FT and SF to SS that allow comparisons between tests in patients with glaucoma and healthy subjects with potential utility both for research and clinical purposes. In the future, it would also be valuable to develop nomograms for the recently introduced SITA Faster strategy[33] that may be used broadly by clinicians.

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