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CLINICAL INVESTIGATION

Reproducibility and reliability of retinal and optic disc measurements obtained with swept-source optical coherence tomography in a healthy population

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Abstract

Purpose To analyze the reproducibility of macular and peripapillary thickness measurements, and optic nerve morphometric data obtained with Triton Optical coherence tomography (OCT) in a healthy population.

Study design Observational cross sectional study.

Material and methods A total of 108 eyes underwent evaluation using the Triton Swept Source-OCT. A wide protocol was used and measurements in each eye were repeated three times. Morphometric data of the optic nerve head, full macular thickness, ganglion cell layer (GCL) and retinal nerve fiber layer thickness (RNFL) were analyzed. For each parameter, the coefficient of variation (COV) and the intra-class (ICC) correlation values were calculated.

Results Measurements were highly reproducible for all morphometric measurements of the optic disc, with a mean COV of 6.36%. Macular full thickness showed good COV and ICC coefficients, with a mean COV value of 1.00%. Macular GCL thickness showed a mean COV value of 3.06%, and ICC higher than 0.787. Peripapillary RNFL thickness showed good COV and ICC coefficients, with a mean COV value of 8.31% and ICC higher than 0.684. The inferotemporal sector showed the lowest ICC (0.685).

Conclusions Triton OCT presents good reproducibility values in measurements corresponding to retinal parameters, with macular measurements showing the highest reproducibility rates. Peripapillary RNFL measurements should be evaluated with caution.

Keywords Coefficient of variation · Reproducibility · Swept source · Optical coherence tomography

Introduction

In the last decade, optical coherence tomography (OCT) devices have become an essential tool in the clinical evaluation of ophthalmological patients. OCT imaging is essential for the diagnosis, follow up and treatment of patients suffering from vitreoretinal [1] or retinochoroidal conditions [2, 3], as well as glaucoma [4] and other optic nerve pathologies [5, 6]. OCT also plays an important role in the diagnosis, monitoring and controlling of neurodegenerative diseases, such as Multiple sclerosis [7–9], Parkinson's disease [10, 11] and Alzheimer's disease [12, 13].

Spectral domain OCT devices have shown good reproducibility values of macular and peripapillary measurements. Several studies suggest higher reproducibility rates for Spectralis OCT (Heidelberg Engineering) over Cirrus high definition (HD) (Carl Zeiss AG) devices in pathologies such as glaucoma [14], multiple sclerosis [15] and Parkinson's disease [16].

Current research focuses on the ability of new Swept source (SS) domain OCT devices to detect retinal and choroidal changes in patients with vitreoretinal pathology, glaucoma and neurodegenerative processes. SS-OCT technology

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uses longer wavelengths [17], obtains widefield B-scans (12 mm vs 6–9 mm with conventional Spectral domain OCT) and more accurate three dimension (3D) imaging of the vitreous, retina, and choroid than those obtained by Spectral domain devices [18]. Additionally, wide scans make it possible to present the optic nerve and macula in the same scan, which allows a faster evaluation.

There are very few studies concerning the reliability of SS-OCT devices. Very recent research suggests a higher reproducibility of SS-Triton OCT (Topcon) compared to Spectralis when obtaining measurements of the corneoscleral area [19]. Macular measurements have also proved highly reproducible using Triton OCT but poor agreement was shown between this device and other Spectral domain devices [20].

In the present study we have analyzed the repeatability and reliability of macular and peripapillary thickness measurements as well as optic nerve morphometric data obtained with Triton OCT in a healthy population. To the best of our knowledge, this is the first study assessing the repeatability of measurements of different retinal layers (including the ganglion cell layer) using this technology.

Methods

Healthy individuals were included in this cross-sectional and observational study. All procedures adhered to the tenets of the Declaration of Helsinki, the experimental protocol was approved by the Ethics Committee of Miguel Servet Hospital and all participants provided written informed consent to participate in the study.

All individuals with significant refractive errors (>5 diopters of spherical equivalent refraction or 3 diopters of astigmatism), intraocular pressure ≥21 mmHg, media opacifications (nuclear colour/opalescence, cortical or posterior subcapsular lens opacity ≥1 according to the Lens Opacities Classification System (LOCS) III system, concomitant ocular diseases (including history of glaucoma or retinal pathology) and systemic conditions that could affect the visual system were excluded from the study. All participants underwent a complete ophthalmologic evaluation that included pupillary, anterior segment, and fundoscopic examinations to discard any suspicious signs of pathology of the retina/optic nerve/choroid; assessment of best-corrected visual acuity relative to the Snellen scale and structural analysis of the retina and optic nerve using SS-OCT technology. All OCT scans were carefully examined, subjects with suspicious results suggesting retinal or optic nerve alterations were excluded from the study. Additionally, morphometric data of the optic nerve head were also assessed and subjects with cup/disc area ratio >0.5 were excluded to avoid recruiting individuals with subclinical glaucomatous damage.

Structural measurements of the retina and optic nerve were obtained using the Deep Range Imaging (DRI) Triton SS-OCT device which uses a tunable laser as a light source to provide a 1,050 nm centered wavelength. This device reaches a scanning speed of 100,000 A-scans per second, yielding 8 µm axial and 20 µm transverse resolution in tissue. The 3D(H) Macula + 5 LineCross protocol (Wide protocol) was used in this study. This protocol provides a fast evaluation of the macular & peripapillary areas. It performs a 12.0 × 9.0 mm 3D scan plus a double 9.0 mm radial scan (with an overlap of 8 linear scans in the center) of the macular and peripapillary areas providing measurements of the 9 macular areas of the Early Treatment Diabetic Retinopathy Study (ETDRS scan), six macular sectors and the peripapillary retinal nerve fiber layer (RNFL) thickness, Temporal-Superior-Inferior-Nasal-Temporal scan (TSINT scan). With the nine ETDRS macular areas (which include a central 1 mm circle representing the fovea, and inner and outer rings measuring 3 and 6 mm in diameter), central and average thickness plus macular volume are analyzed, and full retinal thickness is measured [21]. The macular analysis provides additional data of the ganglion cell layer (*GCL+*, between the RNFL to the inner nuclear layer boundaries; *GCL++*, between the inner limiting membrane –ILM- to the inner nuclear layer boundaries) of 6 macular areas (superotemporal, temporal, inferotemporal, superonasal, nasal and inferonasal). In the peripapillary area the TSNIT provides morphometric data of the optic disc head (disc, cup and rim areas; cup and ring volume; cup-disc ratios and disc diameters) and measurements of the RNFL thickness of 4 quadrants (superior, nasal, inferior and temporal), 6 sectors (superonasal, superotemporal, nasal, temporal, inferonasal and inferotemporal) and 12 clock sectors. The 4 quadrant and 12 clock sector measurements were not analyzed in this study.

All scans were obtained by the same experienced operator and repeated three times in each eye. There was a time delay between acquisitions and the subject position and focus were randomly disrupted, meaning that alignment parameters had to be newly adjusted at the start of each image acquisition. The DRI Triton SS-OCT provides a quality scale in the image to indicate the signal strength. The quality score ranges from 0 (poor quality) to 100 (excellent quality). Only images with a score >55 were analyzed; poor quality images prior to data analysis were rejected by the operator and the scan was repeated until good quality was achieved.

All variables were registered in a database created with a commercial database application program (Excell, Microsoft Office). Only one eye from each subject was randomly selected and included in the statistical analysis. Statistical analysis was performed using commercial predictive analytics software (SPSS, version 20.0; SPSS, Inc.). The normality of the sample distribution was confirmed using the

Kolmogorov–Smirnov test. For each parameter, the coefficient of variation (COV) was calculated using 2 different methods: first, as the standard deviation divided by the mean of the measurement value and expressed as a percentage [15, 16]; second, as the square root of the residual mean squared values of the 3 obtained measures, divided by the mean of measurements, and expressed as a percentage (within subject COV). Both results are shown in the tables in the Results section (the first calculation named COV mean -COVm-, the second is named COV squared -COVsq-). Devices with a COV less than 10% are considered to have high reproducibility, and a COV less than 5% indicates very high reproducibility [15]. To assess the reliability of the repeated measurements, the intra-class correlation coefficients (ICC) for absolute agreement were calculated. The ICC interpretation that we used was slight reliability (for values between 0 and 0.2), fair reliability (from 0.21 to 0.4), moderate reliability (values between 0.41 and 0.6), substantial reliability (values from 0.61 to 0.8), and almost perfect reliability (values of 0.81 and higher).

Results

One hundred and eight eyes of 108 healthy subjects with a mean age of 48 ± 3.14 years (range: 18-80 years) were included in the study. Male/female ratio was over 1:1 (52 males, 56 females). None of the individuals in the study presented any ophthalmic disease or systemic processes that could affect ocular measurements.

Macular ETDRS thickness showed good COV and intra-class correlation coefficients, with a mean COV value of 1.00 ± 2.68% and ICC higher than 0.838. The inner nasal thickness value showed the lowest variability (COV = 0.35 ± 0.44% and ICC = 0.994) (Tables 1, 2). Both calculations for COV (Table 2).

Table 1 Mean coefficient of variation and standard deviation between parenthesis for the different obtained measurements with deep range imaging (DRI) Triton optical coherence tomography (OCT) in healthy subjects

Parameters	Mean COV (SD)
Morphometric disc parameters	6.36 (12.06)
Macula ETDRS	1.00 (2.08)
Macula GCL+	3.06 (7.71)
Macula GCL++	2.67 (7.34)
RNFL	8.31 (14.84)
All macular parameters	2.00 (5.01)

ETDRS Early Treatment Diabetic Retinopathy Study, *GCL* ganglion cell layer, *RNFL* retinal nerve fiber layer, *SD* standard deviation, *COV* coefficient of variation

Table 2 Mean full macular thickness, coefficients of variation and intra-class correlation coefficient values as obtained with deep range imaging (DRI) Triton optical coherence tomography (OCT) in healthy subjects

Macular ETDRS measurements	Mean (SD)	COVm (SD)	COVsq (IC 95%)	ICC
Center	241.55 (17.00)	1.25 (1.97)	2.33 (3.15)	0.958
Inner temporal	297.51 (17.10)	1.18 (3.02)	2.96 (4.94)	0.958
Inner superior	310.00 (15.57)	0.61 (1.09)	1.17 (1.80)	0.979
Inner nasal*	311.38 (13.58)	0.35 (0.44)	0.54 (0.77)	0.994
Inner inferior	306.95 (15.55)	0.56 (1.11)	1.19 (2.00)	0.979
Outer temporal	255.31 (18.70)	1.41 (4.04)	3.55 (6.99)	0.984
Outer superior	271.66 (12.86)	0.70 (1.48)	1.59 (2.58)	0.956
Outer nasal	287.15 (12.12)	0.57 (1.26)	1.31 (2.22)	0.963
Outer inferior	262.03 (12.82)	0.85 (2.27)	2.37 (3.90)	0.902
Avg thickness	275.89 (13.43)	0.96 (2.03)	2.12 (3.21)	0.921
Center thickness	199.55 (17.35)	2.64 (4.25)	5.09 (6.97)	0.839
Total volume	7.80 (0.38)	0.96 (2.03)	2.12 (3.22)	0.921

The asterisk shows the sector with the highest reproducibility and reliability values

ETDRS Early Treatment Diabetic Retinopathy Study, *SD* standard deviation, *COVm* mean coefficient of variation, *COVsq* within subject coefficient of variation, *ICC* intra-class correlation coefficient

Macular GCL+ and GCL++ thicknesses showed good repeatability with a mean COV of 3.06 ± 7.71% and 2.67 ± 7.34%, and ICC of 0.787 and 0.934, respectively. The inferonasal thickness value showed the lowest variability for GCL+ measurements (COV = 1.99 ± 4.83% and ICCt = 0.919). GCL++, however, showed the lowest variability in the inferior thickness value (COV = 1.57 ± 3.39% and ICC = 0.984) (Tables 1, 3). Both calculations for COV can be observed in Table 3.

The results for all morphometric measurements of the optic disc were highly reproducible, with a mean COV of 6.36 ± 12.06%. Linear Cup-Disc Ratio, Vertical Cup-Disc Ratio, Vertical Disc Diameter and Horizontal Disc Diameter showed the highest reproducibility values (COV < 5%). ICC differed among optic disc measurements, Vertical Disc Diameter demonstrated the lowest (0.536) and Cup volume the highest ICC (0.983). The Linear Cup-Disc Ratio showed the lowest variability (COV = 3.41% and ICC = 0.965) (Tables 1, 4). Calculations for COV are listed in Table 4.

Peripapillary RNFL thickness showed good repeatability, with a mean COV of 8.31 ± 14.84% and ICC higher than 0.684 (Tables 1, 4). Total thickness showed the lowest variability (COV = 5.74 ± 11.13% and ICC = 0.791). Inferonasal and inferotemporal sectors showed moderate reproducibility (COV =11.36 and 10.55% respectively). The inferotemporal sector showed the lowest ICC (0.685).

Table 3 Mean ganglion cell thickness, coefficients of variation and intra-class correlation coefficient values as obtained with deep range imaging (DRI) Triton optical coherence tomography (OCT) in healthy subjects

	Mean (SD)	COVm (SD)	COV sq (IC 95%)	ICC
Macular GCL+				
Total	71.41 (8.69)	2.26 (6.00)	6.41 (10.02)	0.882
Superotemporal	69.15 (10.92)	4.05 (11.57)	8.86 (19.20)	0.859
Superior	70.59 (8.59)	2.85 (7.58)	7.99 (12.81)	0.788
Superonasal	75.78 (9.73)	2.43 (5.41)	7.13 (8.51)	0.865
Inferonasal*	74.31 (10.90)	1.99 (4.83)	6.74 (7.92)	0.919
Inferior	68.36 (9.20)	2.91 (6.40)	7.32 (11.45)	0.873
Inferotemporal	70.26 (11.29)	4.99 (12.17)	9.16 (19.21)	0.859
Macular GCL++				
Total	103.36 (14.29)	1.97 (5.23)	3.57 (8.37)	0.975
Superotemporal	90.64 (16.48)	4.26 (12.06)	6.75 (19.49)	0.947
Superior	103.85 (15.17)	2.15 (7.01)	4.28 (11.79)	0.968
Superonasal	114.68 (14.02)	1.88 (5.60)	4.14 (9.13)	0.954
Inferonasal	116.04 (14.55)	2.12 (6.02)	4.77 (9.83)	0.944
Inferior*	103.23 (12.47)	1.57 (3.39)	2.63 (5.48)	0.984
Inferotemporal	92.81 (16.42)	4.76 (12.07)	7.30 (18.42)	0.935

The asterisk shows the sector with the highest reproducibility and reliability values

GCL ganglion cell layer, *SD* standard deviation, *COVm* mean coefficient of variation, *COVsq* within subject coefficient of variation, *ICC* intra-class correlation coefficient

Table 4 Mean morphometric disc values and retinal nerve fiber layer thickness, coefficients of variation and intra-class correlation coefficient values as obtained with deep range imaging (DRI) Triton optical coherence tomography (OCT) in healthy subjects

Morphometric disc parameters	Mean (SD)	COVm (SD)	COVsq (IC 95%)	ICC
Disc area	2.03 (0.49)	6.03 (11.41)	16.82 (18.42)	0.726
Cup area	0.87 (0.50)	9.62 (16.86)	24.32 (26.78)	0.910
Rim area	1.16 (0.39)	7.61 (12.39)	19.86 (20.42)	0.822
Cup volume	0.20 (0.15)	9.48 (22.95)	14.19 (37.88)	0.983
Rim volume	0.17 (0.08)	7.13 (12.25)	13.89 (21.79)	0.968
Cup-disc area ratio	0.41 (0.18)	6.42 (12.31)	14.23 (20.69)	0.956
Linear cup-disc ratio*	0.62 (0.15)	3.41 (6.77)	7.32 (11.43)	0.965
Vertical cup-disc ratio	0.61 (0.14)	5.85 (8.96)	9.73 (14.78)	0.931
Vertical disc diameter	1.69 (0.28)	4.07 (9.62)	13.90 (16.50)	0.536
Horizontal disc diameter	1.61 (0.23)	4.07 (7.14)	10.44 (11.99)	0.707
Peripapillary RNFL				
Total*	100.32 (16.62)	5.74 (11.13)	10.64 (17.28)	0.791
Temporal	75.15 (15.84)	7.44 (13.87)	14.64 (20.82)	0.750
Superotemporal	135.53 (28.77)	8.78 (15.72)	14.20 (24.59)	0.752
Superonasal	109.76 (31.21)	6.08 (9.55)	10.81 (16.01)	0.946
Nasal	82.24 (17.37)	8.24 (13.94)	11.53 (22.42)	0.869
Inferonasal	120.84 (34.31)	11.36 (21.09)	18.83 (33.48)	0.787
Inferotemporal	140.94 (32.33)	10.55 (18.58)	16.37 (28.80)	0.685

The asterisk shows the measurement with the highest reproducibility and reliability values

RNFL retinal nerve fiber layer, *SD* standard deviation, *COVm* mean coefficient of variation, *COVsq* within subject coefficient of variation, *ICC* intra-class correlation coefficient

When the nasal and temporal sectors were compared, the nasal sectors showed higher reliability (mean ICC = 0.867) than the temporal sectors (mean ICC = 0.729).

Discussion

In the present study we evaluated the reproducibility and reliability of DRI Triton OCT in a healthy population, using a wide protocol (3D Macular + 5Line cross) which performs in one scan a complete analysis of the macular area and the optic nerve. Measurements of the macular area (total thickness and GCL) the RNFL and morphometric data of the optic disc head were analyzed. The ETDRS measurements of total macular thickness presented the lowest COV among these measurements, whereas the inner nasal sector of the ETDRS ring showed the highest reproducibility and reliability values. Ganglion cell measurements also showed very high reproducibility (COV <5% in all measurements) and reliability was at least substantial (ICC from 0.61 to 0.80). Compared to GCL+ measurements, GCL++ presented higher reliability (ICC > 0.90). Peripapillary RNFL measurements presented good reproducibility rates, albeit lower than macular measurements. The inferonasal and inferotemporal sectors showed the lowest reproducibility. Morphometric data of the optic disc head presented good reproducibility (COV < 10%) with the linear cup-disc ratio showing the best reproducibility and reliability.

To the best of our knowledge, this is the first study assessing the reliability of full retinal, ganglion cell layer and RNFL thickness as well as morphometric measurements of the optic nerve head obtained with SS Triton OCT. There are a few studies evaluating the reproducibility of Triton OCT and most are focused on the comparison between that and other Spectral domain OCT devices [19, 20, 22]. Bahrami et al. demonstrate the good repeatability of Triton measurements of central macular thickness in both healthy subjects and patients with macular pathology [20]. Despite the fact that no differences in reproducibility values between the different devices were found, COV and ICC were not calculated and thus, reproducibility and reliability of Triton OCT could not be accurately analyzed. Similar results are obtained in the study by Munk et al. that compares the retinal capillary plexus measurements obtained with SS and Spectral domain OCT devices [22]. Even though no differences were found between the different devices, no data about COV is presented.

A recent study analyzing the reproducibility values of muscular and scleral insertion measurements obtained with Spectral domain and SS Triton OCT shows higher reproducibility rates with Triton OCT [19]. Our study did not compare reproducibility measurements between different OCT devices, however, retinal and optic disc measurements are analyzed, which provides new information about the performance of DRI Triton OCT. Macular measurements (including the ganglion cell layer) and peripapillary RNFL thickness are especially important, not only in retina and glaucoma studies, but also in the evaluation of neurodegenerative diseases [10, 23–25].

Based on the results of the current study, morphometric measurements of the optic disc head and the peripapillary RNFL thickness showed the lowest reproducibility. Moreover, we observed that measurements of the temporal sectors of the peripapillary RNFL showed lower reproducibility values compared to the nasal sectors, a potential problem in the evaluation of patients with neurodegenenerative diseases, where the temporal quadrant is usually affected first [5].

In our study, macular ETDRS measurements presented the lowest COV (1.00%) whereas the mean COV of all macular parameters was 4 times lower than that of the RNFL thickness. This observed difference in reproducibility rates between retinal areas (macular vs peripapillary) might be inherent to the 3D Macular + 5Line cross protocol. The Wide protocol obtains macular and peripapillary measurements in one single scan, but the focus area is set on the fovea (the patient is looking at a central light signal). This might cause the areas closer to the focus area (macular measurements) to have higher reproducibility rates compared to those areas situated in the periphery (optic disc measurements). However, optic disc measurements still showed good reproducibility rates and we believe this should not discourage clinicians from using the Wide protocol of Triton OCT. Our results suggest Triton OCT as an excellent device for the evaluation of macular thickness including the segmentation analysis of the GCL. However, optic disc measurements and peripapillary RNFL when obtained with the Wide protocol should be analyzed with caution.

Previous studies analyzing the reproducibility rates of Spectral domain OCT device (Spectralis OCT) show excellent intra- and interobserver rates (over 0.96) in all macular measurements [26] and very good peripapillary reproducibility rates (mean COV range 1.03–2.95%) [16]. We believe that reproducibility rates in the macular area obtained with Triton OCT might be comparable to those of Spectralis OCT. However, using the Wide protocol, reproducibility rates in the peripapillary sectors were lower than Spectral domain devices [16], probably due to the characteristics of the protocol used in our study. More studies analyzing the reproducibility of other peripapillary protocols for Triton OCT would be needed to establish the device's reproducibility potential for optic nerve measurements.

Automated perimetry was not performed as part of the evaluation protocol of our sample. This might have resulted in an important limitation to our study since eyes with subclinical retinal/optic nerve damage might have been included and evaluated as "healthy subjects". However, all participants were first evaluated by two experienced neuroophthalmologists (MS, EGM) for visual acuity (VA) and intraocular pressure (IOP) levels and optic disc

pathological changes (especially glaucomatous changes) by funduscopy using a 78D lens. Additionally, clinical history was carefully evaluated and an exhaustive investigation of suspicious current/past symptoms of retinal/optic nerve damage was carried out by our clinicians. Suspicious OCT results (including morphometric data of the optic nerve head) of retinal/optic nerve/choroidal damage obtained during the evaluation protocol were carefully examined and caused the subject to be excluded from the study. We believe these measurements decreased (although did not eliminate completely) the chances of subclinical retinal/optic nerve/choroidal damage being included in the study.

In conclusion, DRI Triton OCT presents good reproducibility values in measurements corresponding to retinal parameters, with macular measurements showing the highest reliability and repeatability rates. When the 3D Macular + 5Line cross protocol is used peripapillary RNFL measurements should be evaluated with caution, especially the inferotemporal sector, which presented the lowest reliability values. The evaluation of the peripapillary area in this device should be upgraded. Also, a scan that analyzes the RNFL thickness from and to the nasal quadrant should be considered as a future improvement of Triton OCT, since the assessment of the temporal quadrant is of especial importance in the evaluation of neurodegenerative diseases.

Conflicts of interest M. Satue, None; A. Gavin, None; E. Orduna, None; E. Vilades, None; M. J. Rodrigo, None; J. Obis, None; V. Polo, None; J. M. Larrosa, None; L. E. Pablo, None; E. G. -Martin, None.

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