# Repeatability of Manual Subfoveal Choroidal Thickness Measurements in Healthy Subjects Using the Technique of Enhanced Depth Imaging Optical Coherence Tomography

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**Purpose.** The aim of this study was to investigate the repeatability of manual measurements of choroidal thickness in healthy subjects imaged on spectral domain optical coherence tomography (OCT) using the enhanced depth imaging (EDI) technique.

**Methods.** Fifty consecutive, healthy, young, adult volunteers with no known eye disease were enrolled prospectively. Two good-quality horizontal and vertical line scans through the fovea were obtained for each eye. Using the manual calipers provided by the software of the proprietary device, two experienced OCT readers measured the subfoveal choroidal thickness (SFCT) of the horizontal and vertical line scans for all eyes. The readers were masked to each other's readings. Intraobserver, interobserver, and intrasession coefficients of repeatability (CRs) were calculated.

**Results.** Mean (standard deviation [SD]) age of the study subjects was 38 (5) years (range, 30–49 years). Mean (SD) subfoveal choroidal thickness was 332 (90) $\mu$m (right eyes) and 332 (91) $\mu$m (left eyes). Intraobserver CR was approximately 23 (95% confidence interval [CI], 19–26) $\mu$m, whereas interobserver and intrasession CRs were greater at 32 (95% CI, 30–34) and 34 (95% CI, 32–36) $\mu$m, respectively. There was no significant difference in SFCT between all pairs of SFCT measurements except for the two intrasession vertical line scans.

**Conclusion.** A change of >32 $\mu$m was likely to exceed interobserver variability in SFCT. Future studies are required to estimate the repeatability of SFCT measurements in patients with chorioretinal pathology. (*Invest Ophthalmol Vis Sci.* 2011;52:2267–2271) DOI:10.1167/iovs.10-6024

Optical coherence tomography (OCT) is a noninvasive, noncontact imaging modality used to acquire high-resolution, cross-sectional scans of the retina.[1] It has become a valuable tool for the diagnosis and management of chorioretinal disease. In the past, it has been difficult to image deeper structures such as the choroid with this method because of light scatter and decreased resolution and sensitivity with increasing depth. However, new OCT-based techniques for in vivo choroidal imaging have recently been described.[2–5]

Spaide[3] has described the technique of enhanced depth imaging (EDI) OCT. The method involves placing the objective lens of the spectral-domain OCT device (Spectralis; Heidelberg Engineering, Heidelberg, Germany) closer to the eye such that an inverted image is obtained. By performing this maneuver, the deeper structures are placed closer to zero delay, allowing better visualization of the choroid. Its eye-tracking and image-averaging technology, high-speed scanning, reduced noise, and greater coverage of the macular area produces high-resolution, optical, cross-sectional images of the choroid and allows enhanced visualization of pathology. In addition, the thickness of the choroid can be measured at various locations within the macular region.

The ability to reliably image the choroid makes this an emerging area of study, particularly in ocular diseases that are known to involve the choroid or where the choroid is implicated in the pathophysiology of disease. As with any new method of clinical measurement, it is important to validate the repeatability of measurements with the device to understand how precise the tool is and, therefore, be able to distinguish true clinical change from measurement variability or error.

In contrast to retinal thickness measurements on OCT imaging, repeatability of choroidal thickness measurement using EDI OCT in healthy subjects has not been previously studied in detail.[6–12] Only one study has examined the repeatability of choroidal thickness measurements (in 17 subjects) by reporting the correlation coefficient of measurements from two independent observers.[3] However, Bland and Altman[13] suggested that this method can be misleading and recommended the use of within-subject SD as an index of measurement error.

Therefore, the aim of this study was to investigate the repeatability of EDI OCT choroidal thickness measurements within and between observers and OCT scans in healthy subjects using the coefficient of repeatability as recommended by Bland and Altman.[13] The normative data and variations in choroidal thickness across the macular region have been reported in a separate paper.

## Methods

The scans were obtained during a prospective study of EDI OCT choroidal imaging in healthy young adult volunteers with no known eye disease, the results of which are reported in a separate paper (Yeoh J, et al., unpublished data, 2010). The study was approved by the Institutional Review Board (Research Governance Committee, Moorfields Eye Hospital) and was conducted in adherence with the tenets of the Declaration of Helsinki. Fifty healthy subjects gave informed consent to participate in the study and had OCT scans between January and March 2010.

The OCT scans were performed by two retinal specialists (JY [OB1] and WR [OB2]), experienced at performing scans using the spectral-domain OCT device (Spectralis; Heidelberg Engineering). Two high-

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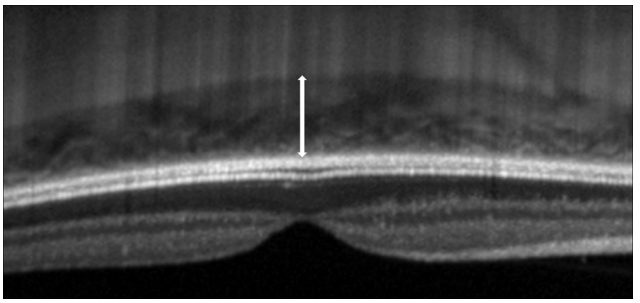

**FIGURE 1.** Horizontal EDI OCT choroidal line scan through the fovea. Measurement of the subfoveal choroidal thickness was performed using the manual calipers of the proprietary device and was taken at the fovea (*arrow*). The *upper end* of the *arrow* delineates the outer choroidal margin, and the *lower end* demarcates the outer border of the RPE hyperreflective band.

quality horizontal (H1 and H2) and vertical (V1 and V2) line scans through the fovea were obtained for each eye. The line scans were saved for analysis after 100 frames were averaged using the automatic averaging and eye tracking features of the proprietary device.

Using the manual calipers provided by the software of the proprietary device, the two retinal specialists measured the SFCT of the two horizontal and two vertical line scans obtained per eye. The SFCT was measured from the outer part of the hyperreflective line corresponding to the base of the RPE to the hyporeflective line or margin corresponding to the sclerochoroidal interface (Fig. 1). The measurements were performed with the readers masked to each other's readings. In addition, one OCT reader (OB1) also repeated the two horizontal SFCT measurements for the right eye (OB1′H1 and OB1′H2), masked to the previous measurements made.

Three types of comparisons were made to calculate the intraobserver, interobserver, and intrasession repeatability, respectively. For estimation of the intraobserver repeatability, two SFCT measurements of the 50 × 2 horizontal line scans of the right eye made by one observer (OB1) were used (OB1H1 vs. OB1′H1; OB1H2 vs. OB1′H2). Observer 1 was masked to the previous choroidal thickness measurements made. Interobserver repeatability was calculated using SFCT measurements for the right and left eyes between the two observers (OB1H1 vs. OB2H1; OB1H2 vs. OB2H2; OB1V1 vs. OB2V1; OB1V2 vs. OB2V2). For estimation of the intrasession repeatability, SFCT measurements of the two horizontal and vertical line scans (H1 vs. H2; V1 vs. V2) made by OB1 and OB2 were used.

Mean (SD) of the differences was calculated. Measurements were compared using the paired-samples *t*-test, and their relationships were assessed using the Pearson's correlation coefficients.

In line with recommendation from Bland and Altman,[14] the difference in SFCT was calculated and plotted against the mean value for all pairs of readings from the two groups being compared. The within-subject SD ($S_w$) derived from the mean square of the differences was used to calculate the coefficient of repeatability (CR) defined by Bland and Altman[14] as $1.96 \times \sqrt{(2S^2_w)}$ or $2.77\ S_w$. In practical terms, the difference between two measurements for the same patient is expected to be less than the CR for 95% of pairs of observations. In addition, the 95% confidence intervals (CIs) for the estimated CR were calculated. For sample sizes of 100, 200, or 400 scans, with each scan subjected to two measurements, the 95% CIs are approximately CR ± CR × 0.139, CR × 0.098, or CR × 0.069, respectively.[15]

A two-tailed paired sample *t*-test was used to determine whether the measurements compared were significantly different. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using data analysis software (SPSS 12.0.1; SPSS Inc., Chicago, IL).

## RESULTS

Data from the scans of both eyes of 50 healthy subjects were analyzed. The mean (SD) age of the study subjects was 38 (5) years (range, 30–49 years). There was an even number of men and women in the study. There were 22 Caucasian, 16 Asian, 8 Oriental, and 4 Afro-Caribbean subjects in the study. The mean (SD) subfoveal choroidal thickness was 332 (90) μm (range, 172–550 μm) and 332 (91) μm (range, 142–563 μm) for the right and left eyes, respectively. The mean (SD) axial length of the subjects' eyes was 24.46 (1.12) mm (range, 22.24–26.96 mm) in the right eye and 24.45 (1.50) mm (range, 22.09–26.89 mm) in the left eye.

Intraobserver, interobserver, and intrasession differences and correlations among the pairs of measurements are summarized in Table 1. All these Pearson's correlations were highly statistically significant ($P < 0.001$). The coefficients of repeatability and the limits of agreement are shown in Table 2.

The intraobserver CR derived from H1 and H2 lines scans (50 × 2 = 100 pairs of measurements) was approximately 23

**TABLE 1.** Summary of Comparisons among Measurements, Observers, and Line Scans

| Type of Comparison | Pairing of Scans | Mean (SD) Difference (μm) | *P* (*t*-test) | Pearson's Correlation Coefficient* |
|---|---|---|---|---|
| Intraobserver (OB1′ − OB1) | OB1′H1 − OB1H1 | +0.4 (11.1) | 0.81 | 0.993 |
| | OB1′H2 − OB1H2 | −1.8 (11.9) | 0.28 | 0.992 |
| Interobserver (OB2 − OB1) | RE OB2H1 − OB1H1 | +2.6 (16.1) | 0.26 | 0.984 |
| | RE OB2H2 − OB1H2 | +4.1 (17.1) | 0.10 | 0.983 |
| | RE OB2V1 − OB1V1 | +0.8 (15.0) | 0.71 | 0.988 |
| | RE OB2V2 − OB1V2 | −2.4 (18.0) | 0.35 | 0.984 |
| | LE OB2H1 − OB1H1 | −1.1 (14.3) | 0.59 | 0.988 |
| | LE OB2H2 − OB1H2 | −2.7 (15.0) | 0.20 | 0.987 |
| | LE OB2V1 − OB1V1 | −1.5 (17.0) | 0.54 | 0.982 |
| | LE OB2V2 − OB1V2 | −3.8 (17.7) | 0.13 | 0.981 |
| Intrasession (Scan 2 − Scan 1) | RE OB1H2 − OB1H1 | +2.7 (18.7) | 0.31 | 0.979 |
| | RE OB1V2 − OB1V1 | +7.6 (16.4) | 0.00 | 0.987 |
| | LE OB1H2 − OB1H1 | +1.4 (20.7) | 0.64 | 0.975 |
| | LE OB1V2 − OB1V1 | +2.8 (15.2) | 0.20 | 0.986 |
| | RE OB2H2 − OB2H1 | +4.2 (18.2) | 0.11 | 0.981 |
| | RE OB2V2 − OB2V1 | +4.4 (14.5) | 0.04 | 0.990 |
| | LE OB2H2 − OB2H1 | −0.2 (17.8) | 0.92 | 0.982 |
| | LE OB2V2 − OB2V1 | +0.5 (13.4) | 0.80 | 0.989 |

LE, left eye; H, horizontal; OB, observer; RE, right eye; V, vertical.
* All $P < 0.001$.

**TABLE 2.** Summary of Limits of Agreement and Coefficients of Repeatability

| Type of Comparison | Grouping of Scans (total *n*) | Mean Difference ($\mu$m) | 95% Limit of Agreement ($\mu$m) | Coefficient of Repeatability ($\mu$m) | 95% CI ($\mu$m) |
|---|---|---|---|---|---|
| Intraobserver (OB1′ − OB1) | H1 (50) | +0.4* | −21.4 to +22.2 | 21.6 | 17.3–25.8 |
| | H2 (50) | −1.8* | −25.1 to +21.4 | 23.3 | 18.7–27.9 |
| Interobserver (OB2 − OB1) | Horizontal (200) | +0.7* | −30.6 to +32.0 | 30.9 | 27.9–33.9 |
| | Vertical (200) | −1.7* | −34.8 to +31.4 | 33.2 | 30.0–36.5 |
| | Right eyes (200) | +1.3† | −31.3 to +33.9 | 32.6 | 29.4–35.8 |
| | Left eyes (200) | −2.3* | −33.6 to +29.0 | 31.5 | 28.4–34.6 |
| Intrasession (Scan 2 − Scan 1) | Horizontal (200) | +2.0* | −34.9 to +38.9 | 37.0 | 33.4–40.7 |
| | Vertical (200) | +3.8‡ | −25.7 to +33.3 | 30.3 | 27.3–33.3 |
| | OB1 (200) | +3.6§ | −31.5 to +38.7 | 35.7 | 32.2–39.2 |
| | OB2 (200) | +2.2† | −29.4 to +33.8 | 31.8 | 28.7–34.9 |

H, horizontal; OB, observer.
* $P > 0.05$; † $P \leq 0.05$; ‡ $P < 0.001$; § $P < 0.005$.

(95% CI, 19–26) $\mu$m. A Bland-Altman plot of difference against mean SFCT showed no significant change in variability for the range of SFCT seen in healthy subjects (200–500 $\mu$m; Fig. 2).

The interobserver CR was approximately 32 $\mu$m (95% CI, 30–34 $\mu$m) for the entire set of H1, H2, V1, and V2 line scans for both eyes ($50 \times 4 \times 2 = 400$ pairs of measurements). The mean (SD) difference in SFCT measurements between the two observers was −0.5 (16.4) $\mu$m, paired *t*-test ($P = 0.53$). The interobserver CR for horizontal line scans, vertical line scans, right eye scans, and left eye scans are shown, separately, in Table 2. A Bland-Altman plot of difference against mean SFCT from the two observers' measurements of all horizontal line scans is shown in Figure 3. A similar scatter distribution is seen for vertical scans.

The intrasession CR was approximately 34 $\mu$m (95% CI, 32–36 $\mu$m) for the entire set of horizontal and vertical line scans for both observers and both eyes ($50 \times 2 \times 2 \times 2 = 400$ pairs of measurements). The SFCT from the second scan was significantly greater than the SFCT from the first scan; the mean (SD) difference was 3 (18) $\mu$m, paired *t*-test ($P = 0.001$). However, this was not the case when only horizontal scans (H2-H1) were compared. Then the mean (SD) difference was 2 (19), paired *t*-test ($P = 0.27$; Table 2). A Bland-Altman plot of difference against mean SFCT from the two scans for all vertical line scans is shown in Figure 4. There was a bias toward greater SFCT from the second vertical scan compared with the first.

## DISCUSSION

Our study showed that the mean SFCT in healthy subjects was 332 $\mu$m (range, 142–563 $\mu$m). In one histologic study, choroidal thickness in healthy maculae ranged from 84 to 193.5 $\mu$m, but, because histologic analysis is an invasive technique with shrinkage of tissue on fixation, it is not directly comparable to our OCT study.[16] Margolis and Spaide[17] used the same EDI OCT technique we used in our study and reported a mean (SD) SFCT of 287 (76) $\mu$m in healthy subjects. However, the mean age of their participants was 50.4 years compared with a mean age of 38 years in our study. Given that age is thought to be negatively correlated with SFCT, this may account for the difference in mean SFCT measurements between the two studies.[17]

This study also provided an estimate of the repeatability of manual SFCT measurements using the spectral-domain OCT device (Spectralis; Heidelberg Engineering) in healthy subjects. These results showed that the intraobserver CR was approximately 22 to 23 $\mu$m, whereas interobserver and intrasession CRs were greater at approximately 32 to 37 $\mu$m. There was no significant difference in SFCT between all pairs of measurements except for the two intrasession vertical line scans.

Menke et al.[18] studied the reproducibility of retinal thickness measurements in healthy persons using the spectral-domain OCT device (Spectralis; Heidelberg Engineering). They showed excellent intrasession reproducibility with almost no difference in retinal thickness measurements for all nine Early Treatment Diabetic Retinopathy Study areas. The mean difference between measurements was approximately 1 $\mu$m. The low variability was thought to be due to the eye-tracking features during scanning, use of the follow-up scanning protocol, improved resolution, imaging speed, scan coverage, and retinal segmentation algorithms. Direct comparison between the Menke et al.[18] study and our study cannot be made for the

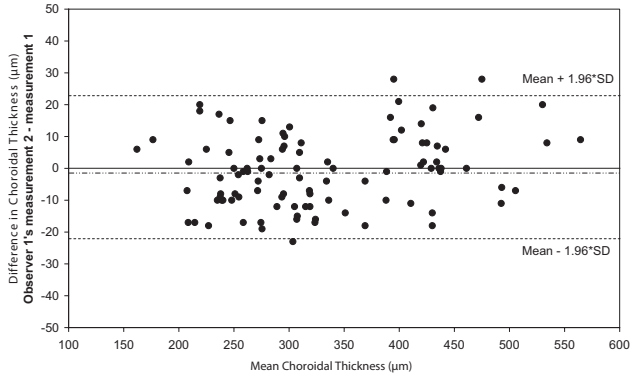


**FIGURE 2.** Bland-Altman plot of difference against mean SFCT showed no significant change in intraobserver variability for the range of SFCT measurements seen in healthy subjects. *Dashed lines*: mean difference and 95% limits of agreement.

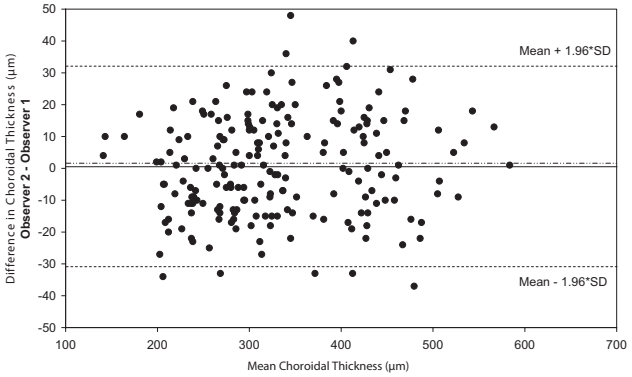


**FIGURE 3.** Bland-Altman plot of difference against mean SFCT showed no significant change in interobserver variability for the range of SFCT measurements for all horizontal line scans. *Dashed lines*: mean difference and 95% limits of agreement.

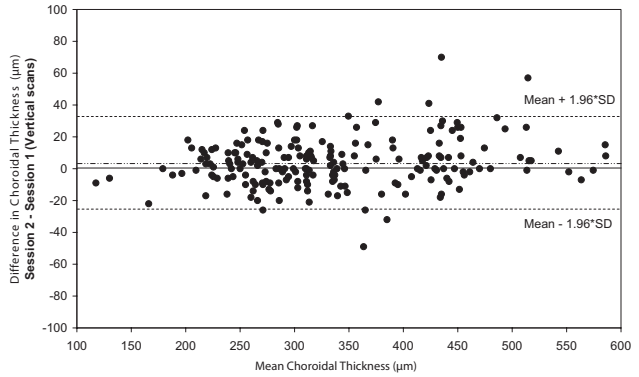


**FIGURE 4.** Bland-Altman plot of difference against mean SFCT for the range of intrasession SFCT measurements for all vertical line scans. *Dashed lines*: mean difference and 95% limits of agreement.

following reasons. The resolution of the choroidal images might not have been as good as the retinal images taken with the spectral-domain OCT device (Spectralis; Heidelberg Engineering). In addition, a software algorithm for choroidal segmentation does not yet exist so our measurements were taken manually. Repeatability studies for retinal thickness have usually used segmentation algorithms rather than manual measurements and vary considerably with regard to the research and statistical methodology used, making comparison difficult.[6–8,10–12]

Spaide et al.[3] briefly reported good interobserver repeatability when measuring SFCT with EDI OCT in a group of volunteers with no known eye disease.[3] In this small group of subjects, there was a highly significant correlation between the measurements performed by the two observers ($r = 0.93$ OD, $r = 0.97$ OS; $P < 0.001$ for both). We also report good interobserver repeatability, though comparison is difficult because of the different statistical methodology used. We are not aware of any other studies that have reported on the repeatability measurements of SFCT using EDI OCT. We postulate that variability in SFCT measurements can arise from factors related to the observer, image quality, adjustments made to alter the contrast of the image, and exact topographic location of the second line scan relative to the first line scan.

One may anticipate less variability in measurements if the same observer measures the same scan twice, even if masked to the previous results. This was true in our study. Similarly, increased variability could be predicted if different observers measured the same scan. Indeed, we found a CR of 23 $\mu$m for intraobserver compared with 32 $\mu$m for interobserver variability, and their 95% CIs did not overlap. There may be a number of reasons for the variability. It is not always easy to distinguish the sclerochoroidal interface on acquired images, which may be related to scan quality or anatomic variation. Some choroidal scans have a distinct hyporeflective line corresponding to the suprachoroidal space, but often this line can be indistinct, leading to measurement variability or error. The placement of the calipers can also vary depending on the magnification of the scan on the screen. Ideally, a magnification of at least 100% should be used to place the calipers precisely at the fovea and measure between the aforementioned landmarks on the scan. In addition, the observers independently used the contrast adjustment software to a variable extent to improve image definition before taking the SFCT measurements. These contributions to both the intraobserver and interobserver measurement variability may be minimized if there is reliable segmentation software to detect choroidal boundaries.

There was a trend for even greater intrasession SFCT variability compared with interobserver and intraobserver measurements. Excluding the vertical scans (significant bias between the two scans), the CR for intrasession comparison was 37 $\mu$m. The 95% CI for this CR was just overlapping with the 95% CI for the CR for interobserver measurements. In addition to the factors described previously, the increased variability in SFCT measurements of the two horizontal or the two vertical scans may be related to misplacement of the line of the OCT slice during the second scan. Measurement error because of scan misplacement might have been minimized if the first scan was set as a reference image and the follow-up protocol was used to acquire the second scan. The intrasession CR might have been lower if this method had been used.

These CR estimates are useful for planning future clinical trials. Such reliable choroidal imaging techniques may allow better understanding and facilitate more in-depth studies of the pathology with underlying origins in the choroid or with associated choroidal changes. For example, they may be of benefit in longitudinal clinical studies investigating the pathogenesis of conditions such as neovascular age-related macular degeneration, central serous chorioretinopathy, and idiopathic polypoidal choroidal vasculopathy.[19–21] Future OCT technologies may incorporate choroidal segmentation software to provide more reliable, automated data on choroidal thickness measurements at the macula. However, as seen in neurosensory retina boundary segmentation, OCT readers need to be aware of the potential differences between devices in the software algorithm used to detect choroidoscleral and retinochoroidal boundaries, and the ability of the software to detect these boundaries in OCT images degraded by optical or motion artifacts and pathology.[22,23] Nevertheless, the results of this study help to improve our understanding of the repeatability of manual measurements of SFCT and could help to validate the accuracy and precision of future automated segmentation algorithms.

The strengths of the study include its prospective design, which randomly recruited a large number of subjects with a wide range of choroidal thicknesses. Scans for the subjects were acquired consecutively (intrasession), which minimized the possibility of true change in SFCT caused by fluctuation in choroidal thickness. Such intersession variations in choroidal thickness and blood flow have been reported and may relate to diurnal variation, fluctuations in intraocular pressure, perfusion pressure, and circulating catecholamines.[24–26] A limitation of this study was that scans were acquired from healthy subjects with no ocular pathology and did not reflect those seen in patients in a routine outpatient setting. For instance, the clarity of images in patients could be hindered by ocular pathology such as significant media opacity or masking of choroidal reflectance by epiretinal, intraretinal, subretinal, and choroidal hyperreflective lesions. In addition, some patients have poor fixation because of disease, leading to problems acquiring good-quality scans, making the accurate measurement of SFCT sometimes difficult. However, given the lack of intraobserver or intrasession repeatability studies for EDI OCT and the limited data on interobserver reproducibility, we chose to study healthy subjects. Additional studies are warranted to test the repeatability of choroidal thickness measurements with the spectral-domain OCT device (Spectralis; Heidelberg Engineering) in patients with chorioretinal pathology and in separate scanning sessions using the follow-up protocol.

In conclusion, our results indicate that a change of 23 $\mu$m is likely to represent true change when the same observer measures SFCT in healthy subjects. However, manual measurements of SFCT can vary as much as 37 $\mu$m when EDI OCT scans are repeated within the same session without use of the follow-up protocol. Further studies are required to determine whether these thresholds of SFCT change are also clinically significant.

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