

# Reproducibility of Optical Coherence Tomography in Multiple Sclerosis

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**Background:** Optical coherence tomography (OCT) is a promising new method of quantifying axon thickness in the retinal nerve fiber layer (RNFL) that has been used predominantly by ophthalmologists to monitor glaucoma. Optical coherence tomography is being considered as a potential outcome measure in multiple sclerosis (MS) clinical trials, but no data exist on the reproducibility of this technique in MS centers.

**Objective:** To determine the reproducibility of OCT measurement of mean RNFL thickness in the undilated eyes of healthy control subjects and patients with MS.

**Design:** Prospective analysis of 4 healthy controls to determine interrater, intrarater, and longitudinal reproducibility. Cross-sectional analysis of 3 cohorts of patients with MS (n=396) and healthy controls (n=153).

**Setting:** Multiple sclerosis clinics at 3 academic medical centers.

**Patients or Other Participants:** Healthy controls and patients with MS.

**Main Outcome Measure:** Thickness of RNFL.

**Results:** We found excellent agreement with respect to interrater (intraclass correlation [ICC], 0.89), intrarater (ICC, 0.98), and intervisit (ICC, 0.91) results. Mean RNFL thickness did not vary significantly among research centers for patients with MS (93, 92, and 90  $\mu\text{m}$ ) or among healthy controls (103, 105, and 104  $\mu\text{m}$ ) by site.

**Conclusions:** We demonstrate that mean RNFL thickness can be reproducibly measured by trained technicians in an MS center using the OCT-3 model. The RNFL measures from cohorts of age-matched controls and patients with MS from 3 different research centers were remarkably similar.

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**O**PTICAL COHERENCE TOMOGRAPHY (OCT) is a noninvasive high-resolution technique that uses near-infrared light to generate cross-sectional tomographic images of tissues,<sup>1</sup> including the retinal nerve fiber layer (RNFL).<sup>2</sup> Optical coherence tomography is used to monitor retinal ganglion cell axon loss in glaucoma, diabetic retinopathy, traumatic optic neuropathy, chiasmal lesions, and optic neuritis.<sup>3-13</sup>

Recently, OCT has been studied in patients with multiple sclerosis (MS) (hereinafter referred to as MS patients), of whom 80% experience visual impairment.<sup>14,15</sup> Decreased RNFL thickness has been demonstrated in patients with a history of optic neuritis.<sup>7,12,16,17</sup> Two studies showed that the eyes without optic neuritis among MS patients have decreased RNFL thickness compared with the eyes of control subjects, suggesting that retinal ganglion cell axonal loss occurs separately from acute

optic neuritis in MS patients.<sup>16,18</sup> In addition, RNFL thickness correlates with low-contrast visual acuity and contrast sensitivity.<sup>16</sup> This suggests that OCT can be used to monitor axonal injury and visual dysfunction in MS and may be a useful outcome measure in clinical trials.<sup>8,12,13,16,19</sup>

Whether reproducibility studies completed on earlier OCT models<sup>20-26</sup> are applicable to the OCT-3 model (Carl Zeiss Meditec, Dublin, California) is unclear because foveal thickness measurements obtained using the prototype OCT scanner and OCT-3 are not directly comparable.<sup>27</sup> The reproducibility of RNFL thickness has been examined using OCT-3 in healthy subjects and cohorts with glaucoma, ocular hypertension, macular edema, and diabetes mellitus,<sup>28-34</sup> but not in MS cohorts. These studies were performed by ophthalmologists on subjects with pharmacologically dilated pupils. All found good reproducibility of RNFL measurements. However, ocular symptoms in

**Table 1. Demographic Characteristics of MS Patients and Healthy Control Cohorts**

	MS Patients				Healthy Control Subjects			
	JHU (n=163) (326 Eyes)	U Penn (n=90) (180 Eyes)	UTSW (n=143) (283 Eyes)	Total (n=396) (789 Eyes)	JHU (n=47) (94 Eyes)	U Penn (n=36) (72 Eyes)	UTSW (n=70) (140 Eyes)	Total (n=153) (306 Eyes)
Age, mean (SD), y	41 (10)	48 (8)	43 (11)	43 (10)	35 (11)	38 (10)	38 (12)	37 (11)
No. (%) female	112 (68.7)	72 (80.0)	105 (73.4)	289 (73.0)	30 (63.8)	28 (77.8)	44 (62.9)	102 (66.7)
Type of MS, No. (%)								
RRMS	135 (82.8)	76 (84.4)	90 (62.9)	301 (76.0)	...	...	...	...
SPMS	16 (9.8)	14 (15.6)	22 (15.4)	52 (13.1)	...	...	...	...
PPMS	12 (7.4)	0	31 (21.7)	43 (10.9)	...	...	...	...

Abbreviations: JHU, The Johns Hopkins University; MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS; U Penn, University of Pennsylvania; UTSW, The University of Texas Southwestern Medical Center; ellipses, not applicable.

MS, including nystagmus, can have an important effect on visual fixation—an essential component in obtaining high-quality OCT scans—and, therefore, present unique challenges in MS patients, with the potential to decrease OCT reproducibility in this cohort. Other possible impediments to the reliable use of OCT in an MS center include the facts that neurology patients do not routinely have their pupils dilated and that neurology office staff are not trained in the use of slitlamp examination. We hypothesized that, despite these issues, OCT could be performed reproducibly in the setting of an MS center.

## METHODS

### SUBJECTS

Interrater, intrarater, and intervisit reproducibility studies were performed at the Johns Hopkins MS Center. We examined both eyes of 4 healthy subjects recruited from the staff of the neurology department. The cross-center comparison was performed using cross-sectional data obtained from age- and sex-matched MS patients (n=396) and healthy controls (n=153) at the MS centers of The Johns Hopkins University (JHU), the University of Pennsylvania (U Penn), and The University of Texas Southwestern Medical Center (UTSW). We included subjects with no history of intraocular surgery, glaucoma, retinal disease, diabetes, or hypertension and who completed informed consent. All MS disease subtypes were included. Data from the initial scans of all patients and controls at each center were included in the cross-center comparison.

### OPTICAL COHERENCE TOMOGRAPHY

The RNFL measurements were obtained using the OCT-3 fast RNFL thickness protocol, which performs 3 consecutive 3.4-mm-diameter circular scans centered on the optic nerve head. In addition, OCT software (OCT 4.0, version A2; Carl Zeiss Meditec) generated a mean RNFL thickness measurement for 360° around the optic disc, 4 retinal quadrants, and 12 clock hour segments (30° for each hour position).

### STUDY PROTOCOL

The RNFL scans were obtained on both eyes of 4 healthy subjects by 3 technicians during 5 consecutive weekly visits. Interrater and intervisit reproducibility were obtained from these data. At visit 3, 1 investigator performed 3 consecutive RNFL scans on

each eye of each subject to determine intrarater reproducibility. All scans were performed without pupil dilation. In the cross-center comparison, 1 OCT scan was obtained of each eye of the MS patients and healthy controls.

## STATISTICAL ANALYSIS

We used the intraclass correlation coefficient (ICC) as a summary measure for interrater, intrarater, and intervisit agreement. The ICC represents the proportion of variance in data explained by between-subject differences; the higher the ICC (maximum value, 1.0), the better the agreement between measures of the same patient. An ICC of less than 0.40 indicates poor reproducibility; of 0.40 to 0.75, fair to good reproducibility; and of greater than 0.75, excellent reproducibility.

In this study design, there was complex nesting, which requires large sample sizes for simultaneous estimates of desired measures; thus, we used random-effects general linear models (Proc MIXED in SAS; SAS Institute Inc, Cary, North Carolina) to compare ICCs between groups of patients, observers, and longitudinally, treating certain factors as fixed and others as random, depending on the ICC being estimated. Variance homogeneity and ICC homogeneity tests were used to validate assumptions made for estimates. We used only 1 eye in each analysis to enable consistency with the literature but present values for each eye. The high correlations between eyes and the relative consistency of the results demonstrate that little additional information was available by incorporating both eyes in the same analysis.

## RESULTS

### SUBJECT CHARACTERISTICS

We studied 8 eyes of 4 healthy subjects for the interrater, intervisit, and intrarater portions of this study. There were 2 men and 2 women, and the mean (SD) age was 23 (3) years (range, 20-27 years). In the cross-center comparison, MS patients and controls across 3 centers did not differ significantly in demographic characteristics (**Table 1**).

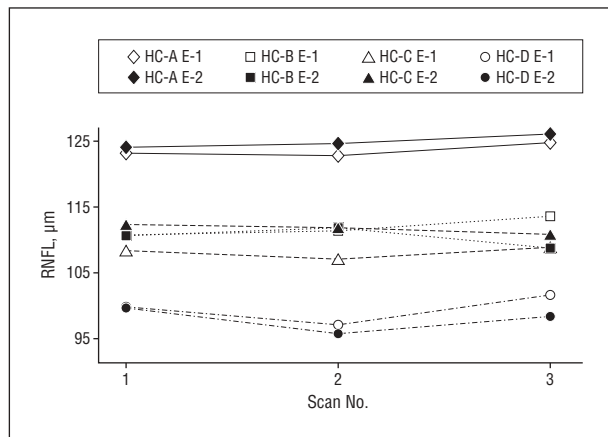
### RNFL THICKNESS

The ICCs were first calculated by combining data from each eye of each subject and indicated excellent agreement (**Table 2**). Quadrant ICCs ranged from 0.66 to 0.98 and were slightly lower than mean RNFL ICCs, which ranged

**Table 2. Optical Coherence Tomographic RNFL Thickness ICCs Calculated Using Both Eyes of Each Subject**

Variable	ICC
<b>Intervisit reproducibility</b>	
Mean RNFL	0.91
Nasal quadrant	0.94
Inferior quadrant	0.85
Superior quadrant	0.75
Temporal quadrant	0.77
<b>Interrater reproducibility</b>	
Mean RNFL	0.89
Nasal quadrant	0.93
Inferior quadrant	0.82
Superior quadrant	0.66
Temporal quadrant	0.72
<b>Intrarater reproducibility</b>	
Mean RNFL	0.98
Nasal quadrant	0.98
Inferior quadrant	0.91
Superior quadrant	0.88
Temporal quadrant	0.96

Abbreviations: ICC, intraclass correlation; RNFL, retinal nerve fiber layer.

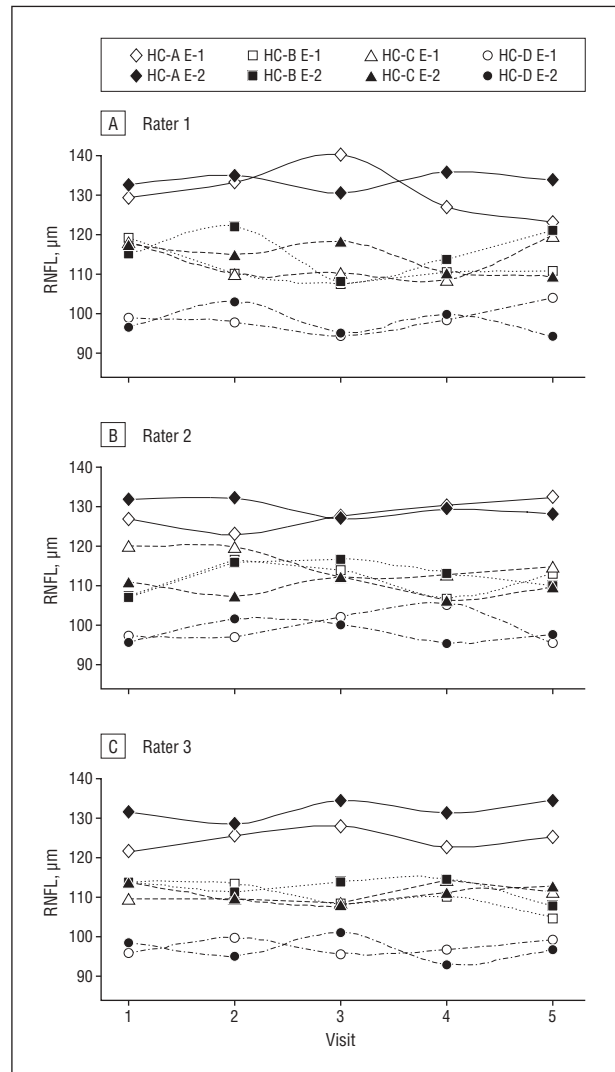


**Figure 1.** Intrarater reproducibility. Mean retinal nerve fiber layer (RNFL) thicknesses from 3 optical coherence tomographic scans of each eye (E-1 and E-2) of healthy control subjects (HC-A to HC-D) obtained by the same rater on the same day.

from 0.89 to 0.98. Intrarater ICCs were highest (**Figure 1**), and intervisit ICCs were also high (**Figure 2**). Although still acceptable, interrater ICCs were the lowest (**Figure 3**). This approach effectively averaged the eyes of each subject, which are highly correlated, and may have slightly overestimated ICCs. When the analyses were repeated considering each eye separately (**Table 3**), ICCs remained high but with wider confidence intervals. Mean (SD) RNFL thickness was remarkably similar among centers for the MS patient and healthy subject cohorts (**Figure 4**).

#### COMMENT

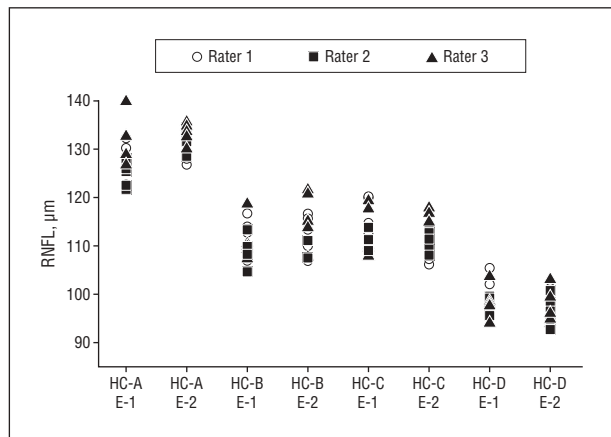
We found that all RNFL measurements showed excellent ICCs when examined for intrarater, interrater, and intervisit reproducibility. Intrarater reproducibility was stronger than intervisit reproducibility, indicating that reproducibility within a given eye on a given day is greater



**Figure 2.** Intervisit reproducibility. Mean retinal nerve fiber layer (RNFL) thicknesses of each eye (E-1 and E-2) of healthy control subjects (HC-A to HC-D) obtained by 3 raters (A, B, and C) at 5 weekly visits.

than reproducibility within a given eye on different days.<sup>21,30</sup> Quadrant thicknesses were more variable than were mean RNFL thickness. The lower ICC for quadrants suggests that quadrant analyses, although potentially more sensitive to subtle changes, will decrease power in clinical trials owing to poorer reproducibility. However, mean RNFL thicknesses are sensitive to abnormalities in MS patients and highly reproducible, making them appropriate to use for comparisons. The major limitation of this portion of our investigation was the small sample size studied.

Our data (Tables 2 and 3) are comparable to previously reported ICCs. One study measuring intervisit reproducibility<sup>30</sup> reported a mean RNFL thickness ICC of 0.83 and ICCs for quadrant thicknesses ranging from 0.62 to 0.81, whereas another group examining intrarater reproducibility<sup>33</sup> found a mean RNFL thickness ICC of 0.95 with quadrant thickness ICCs varying from 0.79 to 0.97. Finally, a recent study of patients with glaucoma<sup>34</sup> found an intrarater mean RNFL thickness ICC of 0.98 and an intervisit mean RNFL thickness ICC of 0.96.



**Figure 3.** Interrater reproducibility. Mean retinal nerve fiber layer (RNFL) thicknesses of each eye (E-1 and E-2) of healthy control subjects (HC-A to HC-D) obtained by 3 different raters.

The most reproducible RNFL measurement in our study was mean thickness, which correlates with previously published results.<sup>30-32</sup> Averaging the mean RNFL thicknesses from several consecutive scans increased the ICC in one report. However, results from averaged and nonaveraged data were similar, indicating that a single scan can provide reliable results.<sup>30</sup> Several groups previously reported quadrant thickness reproducibility. Four studies found that the nasal quadrant was the most variable,<sup>25,32-34</sup> and another found the greatest variability in the superior quadrant, followed by the nasal quadrant.<sup>31</sup> Our results indicate that the nasal quadrant thickness was the most reproducible, whereas superior quadrant thickness was the least reproducible. However, the mean superior quadrant thickness of our healthy subjects was much greater than the mean nasal quadrant thickness (superior, 139 µm, and nasal, 85 µm). A previous study<sup>35</sup> found that macular sector thickness variation increased with increasing macular thickness. This seems to indicate that a similar phenomenon may be seen with RNFL quadrant thicknesses, thus potentially explaining the decreased reproducibility of the superior quadrant in our study.

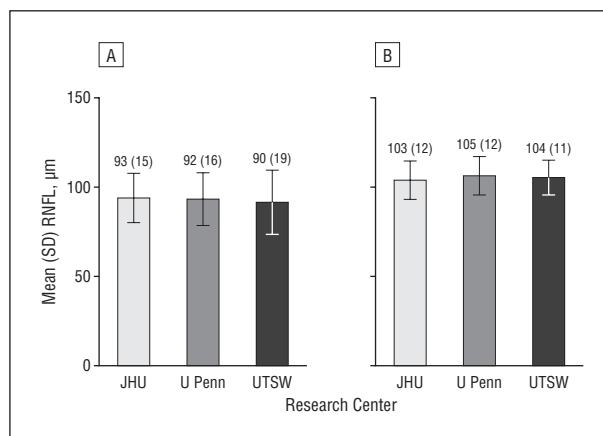
In this study, we did not dilate pupils and found no effect on the quality of the data, which is in keeping with a previous report.<sup>30</sup> Another study investigating whether the technicians' experience affected reproducibility found that inexperienced technicians could generate useful measurements.<sup>25</sup> In our study, 2 technicians had 8 months of OCT-3 experience, whereas 1 technician had 1 month of experience (D.C., M.P., and E.G.-L.). We found that all 3 technicians generated reproducible data.

Other groups have shown higher variation in patients with glaucoma and diabetes compared with healthy subjects.<sup>31,36</sup> To our knowledge, the reproducibility of OCT in MS patients has not been reported previously. Our cross-sectional study was limited because different patients were studied at each site. Although not ideal, the only feasible way to compare large, geographically distant cohorts was to use age-matched subjects with similar demographic characteristics as found in our cohorts. Despite the potential for ocular abnormalities of MS to interfere with obtaining high-quality OCT scans, our

**Table 3. Optical Coherence Tomographic RNFL Thickness ICCs Calculated for Each Eye Separately**

Variable	ICC (95% CI)	
	Right Eye	Left Eye
<b>Intervisit reproducibility</b>		
Mean RNFL	0.88 (0.76 to 0.96)	0.94 (0.87 to 0.98)
Nasal quadrant	0.93 (0.85 to 0.98)	0.95 (0.89 to 0.98)
Inferior quadrant	0.86 (0.71 to 0.95)	0.86 (0.73 to 0.95)
Superior quadrant	0.43 (0.18 to 0.73)	0.80 (0.62 to 0.93)
Temporal quadrant	0.78 (0.60 to 0.92)	0.67 (0.44 to 0.87)
<b>Interrater reproducibility</b>		
Mean RNFL	0.85 (0.72 to 0.93)	0.92 (0.84 to 0.96)
Nasal quadrant	0.92 (0.85 to 0.97)	0.94 (0.87 to 0.97)
Inferior quadrant	0.87 (0.72 to 0.94)	0.78 (0.60 to 0.90)
Superior quadrant	0.16 (-0.09 to 0.47)	0.77 (0.59 to 0.89)
Temporal quadrant	0.72 (0.52 to 0.87)	0.62 (0.38 to 0.81)
<b>Intrarater reproducibility</b>		
Mean RNFL	0.98 (0.89 to 0.99)	0.98 (0.92 to 0.99)
Nasal quadrant	0.98 (0.90 to 0.99)	0.98 (0.92 to 0.99)
Inferior quadrant	0.91 (0.62 to 0.99)	0.93 (0.69 to 0.99)
Superior quadrant	0.74 (0.20 to 0.98)	0.88 (0.53 to 0.99)
Temporal quadrant	0.98 (0.88 to 0.99)	0.93 (0.68 to 0.92)

Abbreviations: CI, confidence interval; ICC, intraclass correlation; RNFL, retinal nerve fiber layer.



**Figure 4.** Cross-center comparison. Mean retinal nerve fiber layer (RNFL) thicknesses from patients with multiple sclerosis (A) and healthy control subjects (B) at 3 research centers. JHU indicates The Johns Hopkins University; U Penn, University of Pennsylvania; and UTSW, The University of Texas Southwestern Medical Center.

cross-sectional data obtained from 3 research centers examining separate MS cohorts were virtually identical. This suggests that RNFL measurements are reproducible within diverse MS patient groups, which is encouraging for the potential use of OCT-3 as an outcome measure in clinical trials. Use of a single model of the same machine also offers advantages over magnetic resonance images obtained using many different models and machine types.

Validation of OCT as an imaging biomarker in MS is important because several aspects of the information it generates are unique. Imaging the RNFL allows direct measurement of the unmyelinated axons of the central nervous system.<sup>37</sup> The capacity to image central nervous system axons quickly and noninvasively, to minimize expense, and to correlate structural abnormalities with visual dys-

function add to the appeal of OCT as an imaging biomarker and outcome measure in clinical trials.<sup>16</sup>

We have demonstrated that OCT RNFL thicknesses obtained in an MS clinic show excellent interrater, intrarater, and intervisit reproducibility in healthy controls. In addition, RNFL measurements from MS and control cohorts from 3 different academic MS centers were remarkably similar. This makes OCT an attractive potential outcome measure for clinical trials of axonal-protective therapeutics and as a potential marker for disease progression in MS patients.

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## REFERENCES

- Huang D, Swanson EA, Lin CP, et al. Optical coherence tomography. *Science*. 1991;254(5035):1178-1181.
- Jaffe GJ, Caprioli J. Optical coherence tomography to detect and manage retinal disease and glaucoma. *Am J Ophthalmol*. 2004;137(1):156-169.
- Kanamori A, Nakamura M, Escano MF, Seya R, Maeda H, Negi A. Evaluation of the glaucomatous damage on retinal nerve fiber layer thickness measured by optical coherence tomography. *Am J Ophthalmol*. 2003;135(4):513-520.
- Medeiros FA, Zangwill LM, Bowd C, Weinreb RN. Comparison of the GDx VCC scanning laser polarimeter, HRT II confocal scanning laser ophthalmoscope, and Stratus OCT optical coherence tomograph for the detection of glaucoma. *Arch Ophthalmol*. 2004;122(6):827-837.
- Medeiros FA, Moura FC, Vessani RM, Susanna R Jr. Axonal loss after traumatic optic neuropathy documented by optical coherence tomography. *Am J Ophthalmol*. 2003;135(3):406-408.
- Monteiro ML, Leal BC, Rosa AA, Bronstein MD. Optical coherence tomography analysis of axonal loss in band atrophy of the optic nerve. *Br J Ophthalmol*. 2004; 88(7):896-899.
- Parisi V, Manni G, Spadaro M, et al. Correlation between morphological and functional retinal impairment in multiple sclerosis patients. *Invest Ophthalmol Vis Sci*. 1999;40(11):2520-2527.
- Trip SA, Schlottmann PG, Jones SJ, et al. Retinal nerve fiber layer axonal loss and visual dysfunction in optic neuritis. *Ann Neurol*. 2005;58(3):383-391.
- Massin P, Girach A, Erginay A, Gaudric A. Optical coherence tomography: a key to the future management of patients with diabetic macular oedema. *Acta Ophthalmol Scand*. 2006;84(4):466-474.
- Costa RA, Skaf M, Melo LA Jr, et al. Retinal assessment using optical coherence tomography. *Prog Retin Eye Res*. 2006;25(3):325-353.
- Savini G, Bellusci C, Carbonelli M, et al. Detection and quantification of retinal nerve fiber layer thickness in optic disc edema using stratus OCT. *Arch Ophthalmol*. 2006;124(8):1111-1117.
- Costello F, Coupland S, Hodge W, et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. *Ann Neurol*. 2006;59(6):963-969.
- Noval S, Contreras I, Rebolledo G, Munoz-Negrete F. Optical coherence tomography in optic neuritis [letter]. *Ophthalmology*. 2007;114(1):200.
- McDonald WI, Barnes D. The ocular manifestations of multiple sclerosis. I: abnormalities of the afferent visual system. *J Neurol Neurosurg Psychiatry*. 1992; 55(9):747-752.
- Warner J, Lessell S. Neuro-ophthalmology of multiple sclerosis. *Clin Neurosci*. 1994;2(3-4):180-188.
- Fisher JB, Jacobs DA, Markowitz CE, et al. Relation of visual function to retinal nerve fiber layer thickness in multiple sclerosis. *Ophthalmology*. 2006;113(2):324-332.
- Trip SA, Schlottmann PG, Jones SJ, et al. Optic nerve atrophy and retinal nerve fiber layer thinning following optic neuritis: evidence that axonal loss is a substrate of MRI-detected atrophy. *Neuroimage*. 2006;31(1):286-293.
- Pulicken M, Gordon-Lipkin E, Balcer LJ, Frohman E, Cutter G, Calabresi PA. Optical coherence tomography and disease subtype in multiple sclerosis. *Neurology*. 2007;69(22):2085-2092.
- Sergott RC. Optical coherence tomography: measuring in-vivo axonal survival and neuroprotection in multiple sclerosis and optic neuritis. *Curr Opin Ophthalmol*. 2005;16(6):346-350.
- Koozekanani D, Roberts C, Katz SE, Herderick EE. Intersession repeatability of macular thickness measurements with the Humphrey 2000 OCT. *Invest Ophthalmol Vis Sci*. 2000;41(6):1486-1491.
- Schuman JS, Pedut-Kloizman T, Hertzmark E, et al. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. *Ophthalmology*. 1996;103(11):1889-1898.
- Massin P, Vicaut E, Haouchine B, Erginay A, Paques M, Gaudric A. Reproducibility of retinal mapping using optical coherence tomography. *Arch Ophthalmol*. 2001;119(8):1135-1142.
- Jones AL, Sheen NJ, North RV, Morgan JE. The Humphrey optical coherence tomography scanner: quantitative analysis and reproducibility study of the normal human retinal nerve fiber layer. *Br J Ophthalmol*. 2001;85(6):673-677.
- Blumenthal EZ, Williams JM, Weinreb RN, Girkin CA, Berry CC, Zangwill LM. Reproducibility of nerve fiber layer thickness measurements by use of optical coherence tomography. *Ophthalmology*. 2000;107(12):2278-2282.
- Villain MA, Greenfield DS. Peripapillary nerve fiber layer thickness measurement reproducibility using optical coherence tomography. *Ophthalmic Surg Lasers Imaging*. 2003;34(1):33-37.
- Carpineto P, Ciancaglini M, Zuppari E, Falconio G, Doronzo E, Mastropasqua L. Reliability of nerve fiber layer thickness measurements using optical coherence tomography in normal and glaucomatous eyes. *Ophthalmology*. 2003;110(1): 190-195.
- Pierre-Kahn V, Tadayoni R, Haouchine B, Massin P, Gaudric A. Comparison of optical coherence tomography models OCT1 and Stratus OCT for macular retinal thickness measurement. *Br J Ophthalmol*. 2005;89(12):1581-1585.
- Hsu SY, Tung IC, Sheu MM, Tsai RK. Reproducibility of peripapillary retinal nerve fiber layer and macular retinal thickness measurements using optical coherence tomography. *Kaohsiung J Med Sci*. 2006;22(9):447-451.
- Lleó-Pérez A, Ortuño-Soto A, Rahhal MS, Martínez-Sorian F, Sanchis-Gimeno JA. Intraobserver reproducibility of retinal nerve fiber layer measurements using scanning laser polarimetry and optical coherence tomography in normal and ocular hypertensive subjects. *Eur J Ophthalmol*. 2004;14(6):523-530.
- Paunescu LA, Schuman JS, Price LL, et al. Reproducibility of nerve fiber thickness, macular thickness and optic nerve head measurements using StratusOCT. *Invest Ophthalmol Vis Sci*. 2004;45(6):1716-1724.
- Pueyo V, Polo V, Larrosa JM, Mayoral F, Ferreras A, Honrubia FM. Reproducibility of optic nerve head and retinal nerve fiber layer thickness measurements using optical coherence tomography. *Arch Soc Esp Oftalmol*. 2006;81(4):205-211.
- Gürses-Ozden R, Teng C, Vessani R, Zafar S, Liebmann JM, Ritch R. Macular and retinal nerve fiber layer thickness measurement reproducibility using optical coherence tomography (OCT-3). *J Glaucoma*. 2004;13(3):238-244.
- Budenz DL, Chang RT, Huang X, Knighton RW, Tielsch JM. Reproducibility of retinal nerve fiber thickness measurements using the Stratus OCT in normal and glaucomatous eyes. *Invest Ophthalmol Vis Sci*. 2005;46(7):2440-2443.
- Budenz DL, Fredette MJ, Feuer WJ, Anderson DR. Reproducibility of peripapillary retinal nerve fiber thickness measurements with Stratus OCT in glaucomatous eyes. *Ophthalmology*. 2008;115(4):661-666.e4. doi:10.1016/j.ophtha.2007.05.035.
- Browning DJ. Interobserver variability in optical coherence tomography for macular edema. *Am J Ophthalmol*. 2004;137(6):1116-1117.
- Polito A, Del Borrello MD, Isola M, Zemella N, Bandello F. Repeatability and reproducibility of fast macular thickness mapping with Stratus optical coherence tomography. *Arch Ophthalmol*. 2005;123(10):1330-1337.
- Frohman E, Costello F, Zivadinov R, et al. Optical coherence tomography in multiple sclerosis. *Lancet Neurol*. 2006;5(10):853-863.