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Cross-platform comparison of retinal layers in MS utilizing a novel open-source automated optical coherence tomography segmentation algorithm

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Disclosures

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- None of the authors have relevant financial disclosures.

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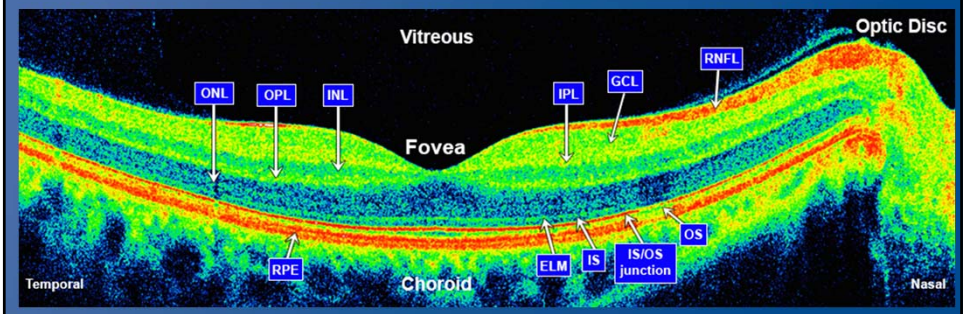
Background

- MS has a predilection for the optic nerve and almost 99% of patients will have optic nerve involvement at autopsy
- Optical coherence tomography (OCT) is a rapid, non-invasive and reproducible method to generate high-resolution, cross-sectional images of the retina



Background

- Early OCT studies in MS focused on peri-papillary retinal nerve fiber layer and total macular volume measurements
- Active MS is associated with more rapid Ganglion cell + inner plexiform layer (GCIP) thinning
- Increased inner nuclear layer (INL) thickness is associated with the development of new T2 lesions, contrast enhancing lesions and EDSS progression
- Primary retinal pathology involving the deeper layers has been described in patients with MS

Ratchford et al. Neurology. 2013 Jan 1;80(1):47-54.
Saidha et al. JAMA Neurol. 2013 Jan;70(1):34-43.
Saidha et al. Brain. 2011 Feb;134(Pt 2):518-33.

Background

- Use of OCT retinal layer measures in MS trials remains limited
- Different OCT platforms at clinical sites and platform specific segmentation algorithms prevent broader utilization
- This situation is analogous to having different MRI scanners at clinical trial sites
- An open-source segmentation algorithm that could be used to segment OCT scans from different OCT platforms could be a solution

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Objective

- To determine cross-sectional and longitudinal agreement of retinal layer thicknesses derived from an open-source, fully-automated, segmentation algorithm, applied to two spectral-domain OCT devices

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Methods

- Cirrus HD-OCT and Spectralis macular scans were acquired on the same day on 68 MS patients and 22 healthy controls
- A subset of 51 subjects with longitudinal scans was also identified
- Scans with low signal strength or obvious artifact were excluded from this study
- Layer segmentation of the OCT data was performed using a novel algorithm detecting 8 layers within the macula

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Methods

- The algorithm works in three stages: pre-processing, pixel classification, and graph-based multi-layer segmentation
- The algorithm utilizes a random forest classifier to determine the probability that each pixel belongs to one of the 9 layer boundaries in a 5x5 mm region centered on the fovea
- Thickness values are averaged within this area

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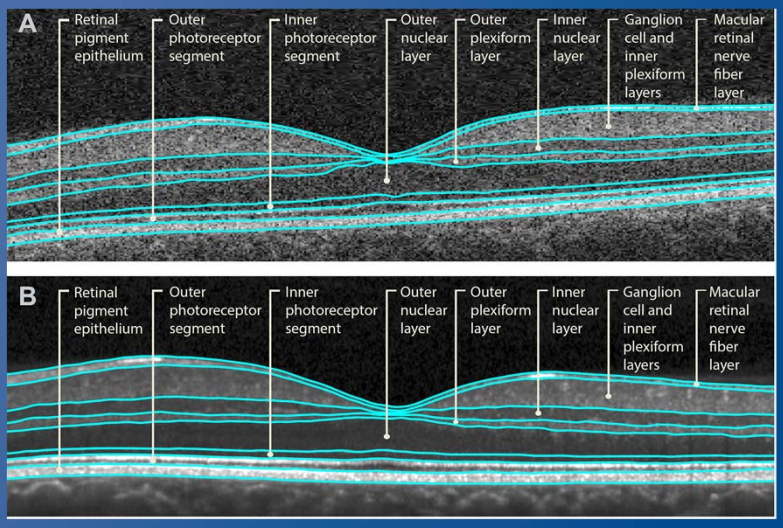
Methods

Cirrus and Spectralis scan segmentation



Methods

Statistical methods

- Bland-Altman analysis to compare measures between the two scanners
- Mean differences with 95% CI, limits of agreement (LOA) with 95% CI, and Bland-Altman plots (differences against average)
- Inter scanner agreement index was calculated for each retinal layer for each subject

  Inter scanner agreement $=1 - (X_a - X_b) / [(X_a + X_b)/2]$
- Longitudinal cohort: modified Bland-Altman analysis adjusted for repeated measures

Methods

Statistical methods

- Mixed effects linear models to calculate the rate of change of layer thickness over time, adjusting for age and gender, and accounting for within-subject, inter-eye correlations
- Exploratory comparison of thicknesses of various retinal layers between MS subjects and healthy controls utilizing similar methods

Results

Study population

Category	Number of subjects	Age (SD)	Sex ratio (Female : male)	Disease duration (SD)
Healthy Controls	22	33.5 (9.1)	13:9	N.A
RRMS	52	41.8 (11.6)	37:15	10.3 (7.3)
SPMS	9	59.5 (6.1)	8:1	27.6 (10.6)
PPMS	7	56.2 (6.4)	4:3	19.7 (12.9)

- The mean follow up duration of the longitudinal cohort was 1.4 ± 0.9 years

Results

Cross-sectional agreement

Layer	Average thickness* (SD)	Mean Difference (95% CI)	Upper LOA (95% CI)	Lower LOA (95% CI)
mRNFL	32.35 (4.38)	4.71 (4.45 to 4.97)	8.22 (7.77, 8.68)	1.20 (0.74, 1.65)
GCIP	65.59 (8.13)	**0.26** (0.04 to 0.48)	3.17 (2.79, 3.55)	-2.65 (-3.03, -2.27)
INL	35.59 (1.81)	**-1.31** (-1.43 to -1.12)	0.20 (0.01, 0.40)	-2.83 (-3.03, -2.63)
INL+OPL	60.59 (3.31)	**-1.09** (-1.33 to -0.86)	2.02 (1.62, 2.43)	-4.21 (-4.62, -3.81)
ONL	63.10 (5.80)	-2.16 (-2.35, -1.97)	0.39 (0.05, 0.72)	-4.71 (-5.05, -4.38)
ONL+PR	108.56 (7.14)	**0.20** (-0.05 to 0.46)	3.61 (3.17, 4.05)	-3.20 (-3.65, -2.76)
RPE	33.32 (1.92)	**0.14** (-0.06 to 0.35)	2.92 (2.56, 3.28)	-2.63 (-2.99, -2.27)

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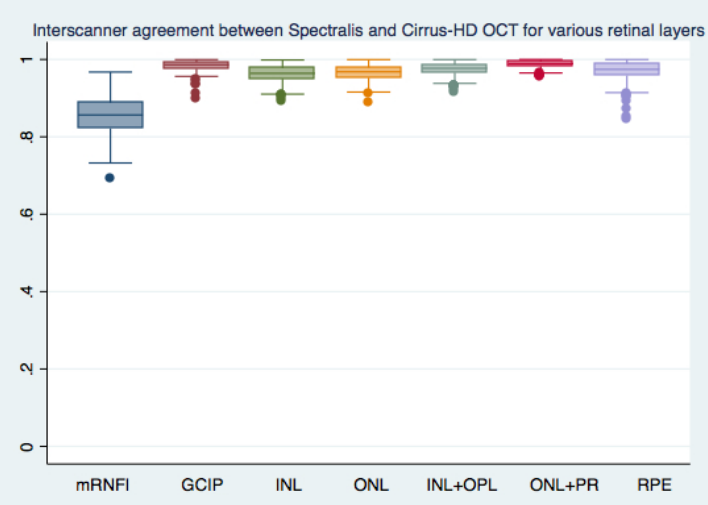
Results

Cross-sectional comparison



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Results

Comparison of MS and healthy controls

- The results of the comparison between MS and HCs were consistent, in terms of magnitude of difference as well as significance, across both platforms for all retinal neuronal layers

Layer	Difference in mean thickness (Spectralis)	p value*	Difference in mean thickness (Cirrus)	p value*
mRNFL	-3.54	**0.001**	-3.62	**<0.001**
GCIP	-9.47	**<0.001**	-9.04	**<0.001**
INL	-0.57	0.241	-0.31	0.498
INL+OPL	-0.87	0.321	-0.66	0.459
ONL	-2.58	0.087	-2.02	0.154
ONL+PR	-2.71	0.14	-2.44	0.172
RPE	-1.39	0.001	-0.92	0.131

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Results

Longitudinal agreement

Layer	Mean change Spectralis (SD)	Mean change Cirrus (SD)	Mean Difference (95% CI)	Upper LOA (95% CI)	Lower LOA (95% CI)
mRNFL	-0.29 (2.11)	-0.09 (1.42)	-0.195 (-0.47 to 0.08)	3.52 (3.04, 4.00)	-3.92 (-4.40, -3.43)
GCIP	-0.54 (2.27)	-0.60 (2.16)	**0.060** (-0.12 to 0.24)	2.45 (2.15, 2.76)	-2.33 (-2.64, -2.02)
INL	-0.046 (0.69)	-0.004 (0.71)	-0.042 (-0.16 to 0.07)	1.56 (1.36, 1.77)	-1.65 (-1.86, -1.44)
INL+OPL	-0.041 (1.59)	-0.056 (1.17)	**0.015** (-0.25 to 0.28)	3.54 (3.09, 4.00)	-3.51 (-3.97, -3.06)
ONL	-0.073 (1.60)	-0.089 (1.33)	**0.016** (-0.17 to 0.20)	2.55 (2.22, 2,87)	-2.52 (-2.85, -2.19)
ONL+PR	0.04 (2.20)	-0.17 (1.91)	0.213 (-0.03 to 0.45)	3.42 (3.01, 3.84)	-3.00 (-3.42, -2.59)
RPE	-0.023 (1.01)	-0.032 (1.05)	**0.009** (-0.15 to 0.17)	2.21 (1.93, 2.50)	-2.20 (-2.49, -1.91)

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Results

Annual longitudinal agreement

Layer	Rate of change of layer thickness - Spectralis Mean (95% CI)		Rate of change of layer thickness - Cirrus Mean (95% CI)	
mRNFL	-0.28 (-0.56, -0.001)		-0.09 (-0.28, 0.09)	
GCIP	-0.59 (-0.89, -0.27)		-0.66 (-0.96, -0.36)	
INL	-0.07 (-0.16, 0.01)		-0.06 (-0.16, 0.03)	
INL+OPL	-0.08 (-0.27, 0.11)		-0.11 (-0.26, 0.04)	
ONL	-0.06 (-0.25, 0.13)		-0.11 (-0.27, 0.05)	
ONL+PR	0.05 (-0.21, 0.31)		-0.16 (-0.39, 0.07)	
RPE	0.004 (-0.12, 0.12)		-0.002 (-0.13, 0.12)	

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Conclusions

Cross-sectional

- Results suggest excellent agreement of all layer measures except the mRNFL at the cohort level
- Comparison of retinal layer measures between MS and healthy controls revealed consistent results across the two scanners

Longitudinal

- Good agreement at the cohort level between the scanners for the GCIP, INL+OPL, ONL and RPE layers longitudinally
- Rates of change of different layers were consistent between the two scanners for all layers except the mRNFL

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Limitations and Future Directions

- A larger study with multiple centers and additional OCT platforms would be informative
- Incorporating methods of registration to the baseline scan may improve agreement between scanners in longitudinal studies
- This new open-source segmentation algorithm could enable us to combine data acquired on different OCT platforms and promote wider utilization of OCT as a measure in trials of neuro-protection in MS

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