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Retinal inner nuclear layer volume; a potential new outcome measure for optic neuritis treatment trials in MS

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BACKGROUND

- The association of peripapillary retinal nerve fibre layer (pRNFL, **Fig 1A**) and ganglion cell-inner plexiform layer (GCIPL, **Fig 1B**) thickness, with neurodegeneration in multiple sclerosis (MS) is well established.[1]
- The potential relationship of the adjoining inner nuclear layer (INL, **Fig 1B**) with inflammatory disease activity is less well understood.[2,3]

OBJECTIVE

To investigate the longitudinal relationship of INL volume changes with inflammatory disease activity.

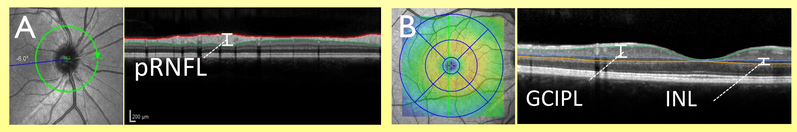
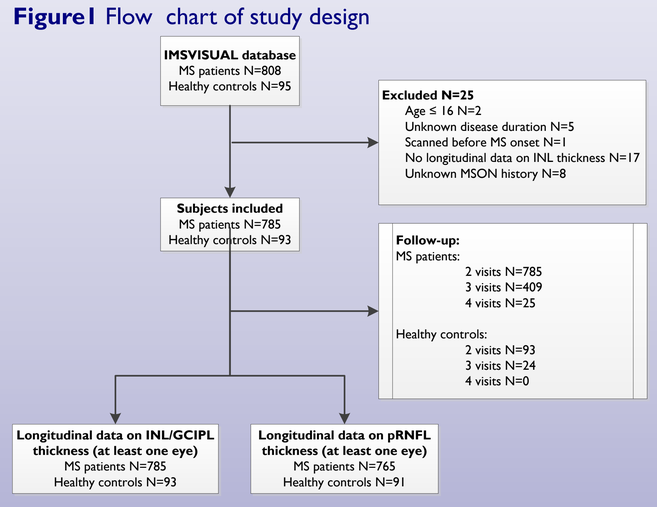


Figure 1. Retinal segmentation of pRNFL (A) and GCIPL and INL (B).

METHODS

Figure1 Flow chart of study design



- A longitudinal, multi-centre study including eleven MS centres.
- Spectral-domain optical coherence tomography (OCT) and clinical data were collected in 785 patients with MS and 97 healthy controls (HCs) between 2010 and 2017 (see **Fig1** and **Table 1**).
- Clinical data included EDSS score, occurring of relapses, including MS-associated optic neuritis (MSON).
- At each centre, automated segmentation of OCT scans was performed to obtain data on the INL and GCIPL volume (mm^3) and pRNFL, thickness (µm).
- (Relative) annualised changes were calculated and generalised estimation equations (GEE) were used to analyse associations with clinical measures.

RESULTS

- Longitudinal changes in INL volume were comparable for MS patients and HCs. Changes in GCIPL and pRNFL were more pronounced in MS (**Fig 2A**).
- An episode of MSON during follow-up (N=61/1562) was associated with a significant increase in INL volume (**Fig 2B**).
- The occurrence of clinical relapses (present in 24.4%) was significantly associated with an increase in INL volume in the subsequent follow-up (**Table 2**).
- INL volume was independent of clinical progression (present in 17.2%) based on change of the EDSS score (**Table 2**).

Table 1. Demographic and clinical characteristics at baseline

	All subjects N=785	Healthy controls N=93
Gender (female, N, %)	536 (68.3%)	59 (63.4%)
Age (years)	41.0 (±12.6)	43.4 (±11.5)
Disease duration (y, median range)	6.4 [0.01 – 45.9]	
EDSS (median [range])	2.0 [0.0-8.0]	
MSON before baseline, N (%)		
No previous MSON	419 (53.4%)	
Unilateral MSON	281 (35.8%)	
Bilateral MSON	85 (10.8%)	
Microcystic macular oedema (N of patients, %)	15/638 (2.5%)	
INL (mm^3)	0.98 (±0.08)	0.96 (±0.09)
GCIPL (mm^3)	1.79 (±0.26)	1.98 (±0.19)
pRNFL (µm)	91.3 (±15.8)	96.8 (±9.1)

Figure2 Relative change in retinal layer thickness with 95% CI for all MS and HC eyes (A) and stratified by MSON- and MSON+ eyes (B).

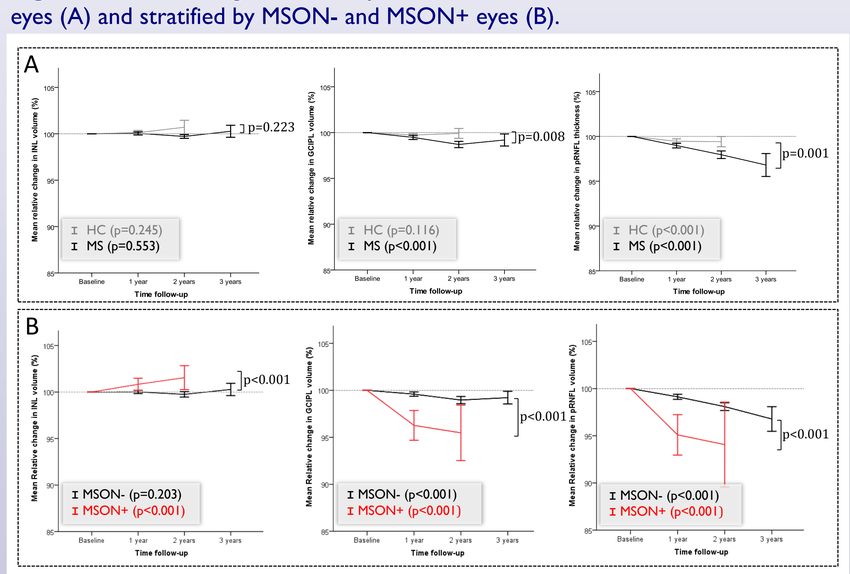


Table 2. The temporal effect of clinical relapses (other than MSON) and disease progression on annualised change in INL, GCIPL and pRNFL thickness

	β	95%CI	p-value*
	Relapse vs no relapse		
INL	0.005	0.001 to 0.01	**0.025**
GCIPL	-0.005	-0.015 to 0.005	0.307
pRNFL	-0.40	-1.57 to 0.77	0.501
	Progression vs no progression		
INL	0.002	-0.003 to 0.007	0.474
GCIPL	-0.007	-0.02 to 0.005	0.250
pRNFL	-0.161	-1.82 to 1.50	0.849

CONCLUSION

- An increase of the INL volume is associated with adjacent inflammation of the optic nerve and retina, and with the occurrence of clinical relapses.
- INL volume changes may be considered as a secondary outcome measure for anti-inflammatory treatment trials.

References

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Disclosures

LJB, DC, BK, RB, RA, MP, RN, LL, TK: have nothing to disclose HZ: received speaking fees from TEVA; EM reports speaking honoraria from Biogen, Genzyme and Novartis and travel reimbursement from Roche for international and national meetings over the last year. Member of the working group of IMSVISUAL. Researcher in OCTIMS study sponsored by Novartis. Grants from the Instituto de Salud Carlos III (JR16/0006); Fundació Marató TV3 (20142030) and GMSI (2016) and Fundació Cellex Barcelona; AV has received compensation for consulting services or speaking honoraria from Novartis, Roche, and Sanofi-Aventis; PA received research grants from Novartis, Biogen Idec, Teva, Merz Pharmaceuticals and travel/accommodation/meeting expenses from Novartis, Teva, Biogen Idec, Merz Pharmaceuticals, Ipsen, Esai and Glaxo Smith Kline; JH received speaker honoraria, travel expenses, and personal compensations from Merck, Biogen, Bayer Healthcare, Sanofi Genzyme and Novartis Pharma; FP served on the steering committee for Novartis OCTIMS study and MedImmune; received speaker honoraria and travel funding from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, and MedImmune; is an academic editor for PLoS One; is an associate editor for Neurology®: Neuroimmunology & Neuroinflammation; has consulted for SanofiGenzyme, Biogen Idec, and MedImmune; and received research support from Bayer, Novartis, Biogen Idec, Teva, Sanofi-Aventis/Genzyme, Alexion, Merck Serono, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research (BMBF Competence Network Multiple Sclerosis), and Arthur Arnstein Stiftung Berlin; OA received grants from the German Research Foundation (DFG), Eugène Devic European Network (EU-FP7), German Ministry of Education and Research, Schaufler Foundation, honoraria for lectures from Almirall, Novartis, Bayer, Genzyme, Teva, Merck Serono, Biogen, Roche, Medimmune, and received travel/accommodation/meeting expenses from Novartis, Bayer Schering, and Merck Serono; XM has received speaking honoraria and travel expenses for scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Pharmaceuticals and Almirall; LBalcer has received consulting fees from Biogen and Genzyme; she has served on a scientific advisory board for Biogen; PV is currently an employee of Genentech and this work was done before and independently of the company; hold stocks in Bionure Inc, Spire Bioventures, Mintlabs and Health Engineering; is academic editor in Multiple Sclerosis and Demyelinating Diseases; and is in the executive committee of the European Association of Systems Medicine; OO reports grant for research from Novartis; grants and personal fees from Biogen-Idec, funding for travel from Biogen-Idec, Genzyme-Sanofi, Merck-Serono, Novartis and Teva Pharmaceutical Industries, outside the submitted work; AP is member of the steering committee for the OCTiMS study (Novartis) and received no consulting fees. He is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. He performed OCT QC for the PASSOS study (Novartis) and received consulting fees.

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