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A composite measure to explore visual disability in primary progressive multiple sclerosis

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Abstract

Background: Optical coherence tomography (OCT) and magnetic resonance imaging (MRI) can provide complementary information on visual system damage in multiple sclerosis (MS).

Objectives: The objective of this paper is to determine whether a composite OCT/MRI score, reflecting cumulative damage along the entire visual pathway, can predict visual deficits in primary progressive multiple sclerosis (PPMS).

Methods: Twenty-five PPMS patients and 20 age-matched controls underwent neuro-ophthalmologic evaluation, spectral-domain OCT, and 3T brain MRI. Differences between groups were assessed by univariate general linear model and principal component analysis (PCA) grouped instrumental variables into main components. Linear regression analysis was used to assess the relationship between low-contrast visual acuity (LCVA), OCT/MRI-derived metrics and PCA-derived composite scores.

Results: PCA identified four main components explaining 80.69% of data variance. Considering each variable independently, LCVA 1.25% was significantly predicted by ganglion cell-inner plexiform layer (GCIPL) thickness, thalamic volume and optic radiation (OR) lesion volume (adjusted R^2 0.328, $p = 0.00004$; adjusted R^2 0.187, $p = 0.002$ and adjusted R^2 0.180, $p = 0.002$). The PCA composite score of global visual pathway damage independently predicted both LCVA 1.25% (adjusted R^2 value 0.361, $p = 0.00001$) and LCVA 2.50% (adjusted R^2 value 0.323, $p = 0.00003$).

Conclusion: A multiparametric score represents a more comprehensive and effective tool to explain visual disability than a single instrumental metric in PPMS.

Keywords: Multiple sclerosis, MRI, OCT, primary progressive, neurodegeneration, visual damage

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Introduction

Impairment of visual acuity and retinal integrity is frequent in patients with primary progressive multiple sclerosis (PPMS) despite the absence of episodes of acute optic neuritis (ON),[1] suggesting that they may be the consequence of primary injury to retinal neurons, as part of the disease process,[2] or secondary damage related to anterior and posterior visual pathway injury, with anterograde and retrograde trans-synaptic degeneration being known causes of retinal damage across different pathologies.[3–5]

Among quantitative measures of visual acuity, low-contrast visual acuity (LCVA), together with contrast sensitivity, shows the greatest ability to capture MS-related visual dysfunction,[6] and it is associated not only with optical coherence tomography (OCT)-derived metrics of retinal integrity but also with magnetic resonance imaging (MRI) measures of damage involving both the anterior[7] and post-geniculate component of the visual pathway.[7–10] Although OCT-derived metrics show stronger correlation with LCVA than MR-derived metrics[6] and have been recently incorporated into MS clinical trials,[11] it remains to be determined whether a cumulative index of visual pathway damage, including MRI parameters, could be a better predictor of visual disability than a single MRI or OCT parameter, offering a more comprehensive tool to explore the physiopathology of VA deficits in PPMS. Therefore, our aim was to investigate the correlation

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between OCT and MRI metrics of visual pathway damage and VA in PPMS patients applying a data-driven composite score.

Methods

Population

Twenty-five PPMS patients and 20 sex- and age-matched controls (CTRLs) were prospectively enrolled. Inclusion criteria for PPMS patients were (1) age between 25 and 65 years, (2) an Expanded Disability Status Scale (EDSS)[12] lower than 6.5 at screening visit, and (3) disease duration lower than 15 years. Exclusion criteria for all participants were (1) neuropsychiatric disorders other than MS, (2) ophthalmological pathologies (i.e. diabetes mellitus or glaucoma), (3) history of alcohol or drug abuse, and (4) contraindications to MRI. Demographic and clinical data are summarized in Table 1.

Standard protocol approvals and patient consents

The study was approved by the local institutional review board and written informed consent was obtained from all participants.

Clinical assessment

VA was assessed as previously described.[13] LCVA scores at 2.50% and 1.25%[6] were entered in the statistical analysis.

Evaluation of visual pathway damage

Different metrics were computed in order to express the damage occurring along the two main segments constituting the visual pathway: the anterior pathway, comprising the retina, optic nerves, chiasm, and optic tracts; and the posterior pathway, comprising the optic radiations and visual cortex, connected by a single synapsis in the midbrain.

Damage of the first-order neuron, located in the retina and projecting to the thalamic lateral geniculate nucleus (LGN), was evaluated through ganglion cell-inner plexiform layer (GCIPL) thickness, retinal nerve fiber layer (RNFL) thickness, optic nerve (ON) and optic tract (OT) diameter measurements. Damage of the second-order neuron, located in the LGN and projecting to the visual cortex, was evaluated through thalamic volume (used as a proxy for LGN volume), optic radiation (OR) volume and fractional anisotropy (FA) measurements. Damage of the third-order neuron, located in the visual cortex, was evaluated through visual cortex volume and occipital lobe cortical lesion (CL) count measurements.

OCT and MRI acquisition

Spectral-domain OCT imaging was performed using Spectralis (Heidelberg Engineering, Heidelberg, Germany; software version 5.6.eye explorer software 1.7.1.0) and processed as previously described.[13] Scans that violated international consensus quality control criteria (OSCAR-IB) were excluded from the analysis.[14,15] Both RNFL and GCIPL thickness were evaluated and included in the statistical analysis as indirect structural markers of axonal and neuronal damage.

MRI was performed using a 3.0 T scanner (Philips Achieva, The Netherlands) with an eight-channel sensitivity encoding (SENSE) phased-array head coil. The MRI protocol included the following sequences: (1) axial dual echo turbo spin echo; (2) high-resolution sagittal three-dimensional (3D)

Table 1. Demographic and clinical characteristics of MS patients and controls.

	PPMS ($n = 25$)	CTRLs ($n = 20$)	p value
Gender (male/female)	11/14	9/11	0.542[a]
Age (range), years	51.8 (32–65)	51.1 (34–63)	0.645[b]
Disease duration, years	8.7 ± 4.8	–	
EDSS median (range)	4.0 (1.5–6.0)	–	
Letters read correctly at 100%	54 ± 5	56 ± 7	0.093
Letters read correctly at 2.5%	31 ± 11	39 ± 12	**0.002**
Letters read correctly at 1.25%	20 ± 12	31 ± 11	**0.0001**

MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; CTRLs: healthy controls; EDSS: Expanded Disability Status Scale; SD: standard deviation.
Statistically significant p values are in bold.
[a]Fisher's exact test.
[b]Mann–Whitney test.
Unless otherwise specified, all values are expressed as mean ± SD.

T1-weighted turbo field echo; (3) twice-refocused spin-echo echo planar imaging with b values of 1000 and 2000 s/mm^2 and 30 directions each; and (4) phase-sensitive inversion recovery.

MRI analysis

ON and OT diameters were measured as previously described[16] (e-Figure 1) and then normalized to head size by multiplying the raw volumes by the SIENAX scaling factor (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA). Probabilistic tractography was performed in order to reconstruct OR fibers using FMRIB Diffusion Toolbox (FDT) from FSL (v5.0.8) (http://www.fmrib.ox.ac.uk/fsl). Seed regions were placed on the LGN and pericalcarine cortex; waypoint masks were drawn in the lateral wall of the occipital horn of the lateral ventricles and exclusion masks were drawn along the midline and anteriorly to the Meyer's loop. Brain T2 and T1 lesion volumes (LVs) were measured as previously described.[9] The reconstructed OR tracts and the white matter (WM) lesion regions of interest (ROIs) were used as masks to calculate FA within ORs lesions and in OR normal-appearing WM (NAWM), OR LV and OR tract volume. OR LV was subtracted from the mask-derived OR tract volume to obtain the final OR tract volume measure. Normalized thalamic volume, visual cortex volume and occipital lobe CL count were assessed as previously described.[13] Further details on the MRI protocol and tractography procedure can be found in Supplemental Material (e-Methods).

Statistical analysis

Data analysis was performed using SPSS 22.0 (SPSS, Chicago, IL, USA). Age and gender differences were tested with Mann–Whitney and Fisher's exact test. An analysis of variance was used to assess between-group differences in terms of clinical, OCT and MRI variables. Statistical significance was defined as $p < 0.05$, Bonferroni corrected for multiple comparisons at $p < 0.004$. To avoid bias related to strong inter-variable correlation, inter-eye average of OCT metrics and left-right average of MRI metrics were entered in the principal component (PCA) and regression analyses. A PCA was applied to OCT/MRI variables and the components eigenvectors were used to calculate a weighted value for the measured metrics and thus obtain a composite score for each identified component and a global PCA-derived score. Linear regression analyses were used to assess binocular LCVA relationship with OCT/MRI-derived metrics and PCA-derived composite scores. Statistical significance was defined as $p < 0.05$,

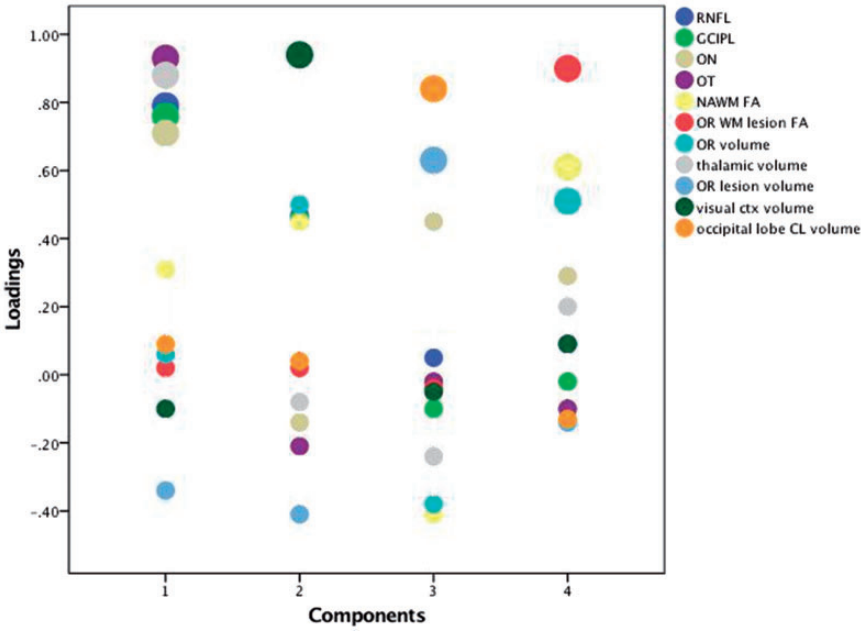

Figure 1. PCA results. Segregation of OCT and MRI metrics in the four principal components with relative loadings. Each variable is color coded. A larger dot indicates the maximum loading attributed to the specific variable from the PCA analysis. PCA: principal component analysis; OCT: optical coherence tomography; MRI: magnetic resonance imaging; RNFL: retinal nerve fiber layer; GCIPL: ganglion cell + inner plexiform layer; ON: optic nerve; OT: optic tract; NAWM: normal-appearing white matter; FA: fractional anisotropy; OR: optic radiation; WM: white matter; CL: cortical lesion.

Bonferroni corrected for multiple comparisons at $p < 0.003$.

Results

Patients' OCT and MRI data are listed in Table 2.

Three out of the 50 MS eyes and two out of 40 CTRLs eyes were excluded from the analysis because they did not fulfill the ophthalmological criteria.

PCA of patients and controls' OCT/MRI metrics identified four components that explained 80.69% of data variance. The first component, which gathered all the variables pertaining to the anterior visual pathway (RNFL thickness, GCIPL thickness, ON and OT diameters, thalamic volume), explained 32.46% of data variance. The second component, which included the visual cortex volume, explained 18.09% of data variance. The third component, which gathered the OR LV and the occipital lobe CL count, explained 15.26% of data variance. The fourth component, which included variables describing the OR damage (OR NAWM FA, OR lesion FA, OR LV), explained 14.88% of data variance. PCA results are displayed in Figure 1.

Considering each variable independently, LCVA 1.25% was significantly predicted by GCIPL thickness, thalamic volume and OR LV (adjusted R^2 0.328, $p = 0.00004$; adjusted R^2 0.187, $p = 0.002$ and adjusted R^2 0.180, $p = 0.002$, Bonferroni corrected). Additional results of the regression analysis for each individual metric are reported in Table 3.

The PCA composite score of global visual pathway damage independently predicted both LCVA 1.25% (adjusted R^2 value 0.361, $p = 0.00001$, Bonferroni corrected) and LCVA 2.50% (adjusted R^2 value 0.323, $p = 0.00003$, Bonferroni corrected).

Among the single-component-derived composite scores, only the anterior visual pathway score significantly predicted LCVA 1.25% (adjusted R^2 value 0.361, $p = 0.00001$, Bonferroni corrected) and LCVA 2.5% (adjusted R^2 value 0.321, $p = 0.00004$, Bonferroni corrected), while the OR damage score, the lesion load score and the visual cortex score were not predictive of LCVA 1.25% (adjusted R^2 value −0.006, $p = 0.388$; adjusted R^2 value −0.007, $p = 0.405$ and adjusted R^2 value 0.053, $p = 0.071$, respectively) and LCVA 2.50% (adjusted R^2 value −0.015, $p = 0.556$; adjusted R^2 value −0.012, $p = 0.487$ and adjusted R^2 value 0.041, $p = 0.099$, respectively).

Discussion

Our results show that an MRI- and OCT-based multiparametric measure can predict VA deficits more effectively than single OCT- and MRI-derived

Table 2. OCT and MR parameters in PPMS and CTRLs.

	PPMS ($n = 25$)	CTRLs ($n = 20$)	p value
RNFL (μm)	86.9 ± 13.6	92.8 ± 12.4	0.040
GCIPL (μm)	66.0 ± 9.4	72.6 ± 6.7	**0.001**
ON diameter (mm)	6.0 ± 0.7	6.2 ± 0.6	0.255
OT diameter (mm)	5.3 ± 0.7	5.8 ± 0.8	0.021
Thalamic volume (ml)	8.89 ± 1.12	10.11 ± 0.92	**0.001**
OR volume (ml)	1.51 ± 0.38	1.66 ± 0.33	0.168
OR NAWM FA[a]	0.44 ± 0.04	0.47 ± 0.03	**0.003**
OR lesion volume (ml)	0.10 ± 0.10	–	–
OR WM lesion FA[a]	0.37 ± 0.06	–	–
Visual cortex signal intensity[b]	0.34 ± 0.06	0.39 ± 0.05	0.011
Occipital lobe CL count	0.43 ± 0.78	–	–

OCT: optical coherence tomography; MRI: magnetic resonance imaging; PPMS: primary progressive multiple sclerosis; CTRLs: healthy controls; RNFL: retinal nerve fiber layer; GCIPL: ganglion cell + inner plexiform layer; ON: optic nerve; OT: optic tract; OR: optic radiation; WM: white matter; NAWM: normal-appearing white matter; FA: fractional anisotropy; OR: optic radiation; CL: cortical lesion; SD: standard deviation.
Statistically significant p values are in bold.
[a]Fractional anisotropy value (adimensional) extracted from white matter region of interest.
[b]Signal intensity values (adimensional eigenvalues) extracted from gray matter region of interest.
Unless specified, all values are expressed as mean ± SD.

Table 3. Regression analysis between LCVA and OCT/MRI metrics.

	LCVA 2.50%		LCVA 1.25%	
	Adjusted R^2	p value	Adjusted R^2	p value
RNFL	0.057	0.064	0.165	0.004
GCIPL	0.156	0.005	0.328	**0.00004**
ON diameter	−0.011	0.475	−0.016	0.573
OT diameter	−0.006	0.395	0.012	0.226
Thalamic volume	0.096	0.023	0.187	**0.002**
OR volume	0.029	0.139	0.021	0.172
OR NAWM FA	0.055	0.069	0.079	0.036
OR lesion volume	0.157	0.005	0.180	**0.002**
OR WM lesion FA	0.157	0.058	0.156	0.059
Visual cortex signal intensity	0.049	0.081	0.061	0.059
Occipital lobe CL count	−0.019	0.649	−0.015	0.560

LCVA: low-contrast visual acuity; OCT: optical coherence tomography; MRI: magnetic resonance imaging; RNFL: retinal nerve fiber layer; GCIPL: ganglion cell + inner plexiform layer; ON: optic nerve; OT: optic tract; OR: optic radiation; WM: white matter; NAWM: normal-appearing white matter; FA: fractional anisotropy; OR: optic radiation; CL: cortical lesion.
Statistically significant p values are in bold.

metrics of visual pathway damage. The global visual pathway score and the anterior visual pathway score showed a similar predictive power in the regression analysis, suggesting that the damage of the anterior visual pathway plays a prominent role in determining visual disability. Even if only a few of the single metric regressions survived the correction for multiple comparisons, the predictive trends highlighted by this analysis deserve a comment. With respect to the anterior visual pathway, the metrics associated with VA were the GCIPL thickness, in line with previous findings,[10] and the thalamic volume. The predictive role of the thalamus might be related to its central position along the visual pathway that makes it susceptible both to anterograde and retrograde trans-synaptic neurodegeneration from anatomically connected structures, although the development of thalamic atrophy might partially derive from the neurodegenerative component of the disease that also drives global brain atrophy development. With respect to the posterior visual pathway, only OR lesion volume was correlated with visual deficit. Although this is a little surprising because of the general paucity of WM inflammatory lesions and predominance of gray matter (GM) pathology in PPMS, it might be partially explained by the small number of CLs detected in the occipital lobe of our patients. In addition, the low contribute of visual cortex volume to visual disability might be explained, at least in part, by the fact that damage to the visual cortex has been primarily reported as a consequence of anterograde degeneration secondary to optic neuritis,[10] which none of our patients had experienced. On the other hand, the lack of clinically evident episodes of optic neuritis does not exclude the presence of anterior visual pathway damage in our cohort that is indeed suggested by the results of our regression analysis.

Other groups have reported that visual dysfunction is related to retinal layer thinning[17] and damage of ORs[9] even in patients with PPMS. However, the use of a composite score including both OCT- and MRI-derived metrics of tissue damage can increase our understanding of the physiopathology of VA deficits in PPMS and provide a measure to better monitor their evolution.

Since each instrumental metric refers to different MS pathological aspects, diverse measures provide complementary information on the contemporaneous involvement of various structures of the same functional system. As a consequence, a composite index provides a better correlate for MS pathological process and its relation to clinical disability, increasing the predictive value of the measure even in small populations.

Although our composite measure was a good predictor of visual disability, it could be further improved by the inclusion of other indices of microstructural damage (i.e. magnetization transfer ratio (MTR) within the visual cortex, ONs and OTs) and would benefit from a validation in a larger MS population.

In particular, considering our small sample size and the consequent risk for overfitting of the model, the replication of our findings in other datasets would increase the external validity of our results.

In summary, our study provides evidence that, similarly to what has been reported for motor disability,[18] a multiparametric score based on different instrumental metrics can explain more comprehensively visual dysfunction rather than a single parameter, since it includes indicators of different MS pathological processes that contribute to clinical deficit.

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Author contributions are as follows: MI had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: MI and MP. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: VP, MP, CS and MI. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: VP, MP and MI. Obtained funding: MI. Study supervision: MI.

Conflicts of interest

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Supplementary material

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