MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Impaired motion perception is associated with functional and structural visual pathway damage in multiple sclerosis and neuromyelitis optica spectrum disorders

Multiple Sclerosis Journal
2022, Vol. 28(5) 757–767
DOI: 10.1177/13524585211032801

Noah Ayadi, Frederike C Oertel, Susanna Asseyer, Rebekka Rust, Ankelien Duchow, Joseph Kuchling, Judith Bellmann-Strobl, Klemens Ruprecht, Alexander Klistorner, Alexander U Brandt, Friedemann Paul and Hanna G Zimmermann

Abstract

Background: Decreased motion perception has been suggested as a marker for visual pathway demyelination in optic neuritis (ON) and/or multiple sclerosis (MS).

Objectives: To examine the influence of neuro-axonal damage on motion perception in MS and neuromyelitis optica spectrum disorders (NMOSD).

Methods: We analysed motion perception with numbers-from-motion (NFM), visual acuity, (multifocal (mf)) VEP, optical coherence tomography in patients with MS ($n = 38$, confirmatory cohort $n = 43$), NMOSD ($n = 13$) and healthy controls ($n = 33$).

Results: NFM was lower compared with controls in MS ($B = -12.37$, $p < 0.001$) and NMOSD ($B = -34.5$, $p < 0.001$). NFM was lower in ON than in non-ON eyes ($B = -30.95$, $p = 0.041$) in NMOSD, but not MS. In MS and NMOSD, lower NFM was associated with worse visual acuity ($B = -139.4$, $p < 0.001$/$B = -77.2$, $p < 0.001$) and low contrast letter acuity ($B = 0.99$, $p = 0.002$/$B = 1.6$, $p < 0.001$), thinner peripapillary retinal nerve fibre layer ($B = 1.0$, $p < 0.001$/ $B = 0.92$, $p = 0.016$) and ganglion cell/inner plexiform layer ($B = 64.8$, $p < 0.001$/$B = 79.5$, $p = 0.006$), but not with VEP P100 latencies. In the confirmatory MS cohort, lower NFM was associated with thinner retinal nerve fibre layer ($B = 1.351$, $p < 0.001$) and increased mfVEP P100 latencies ($B = -1.159$, $p < 0.001$).

Conclusions: Structural neuro-axonal visual pathway damage is an important driver of motion perception impairment in MS and NMOSD.

Keywords: Multiple sclerosis, neuromyelitis optica spectrum disorders, motion perception, retina, vision disorders, optical coherence tomography, visual evoked potentials

Date received: 21 March 2021; revised: 8 June 2021; accepted: 28 June 2021

Correspondence to:
HG Zimmermann
Experimental and Clinical Research Center, Lindenberger Weg 80, 13125 Berlin, Germany.
hanna.zimmermann@charite.de

Noah Ayadi
Susanna Asseyer
Rebekka Rust
Ankelien Duchow
Judith Bellmann-Strobl
Hanna G Zimmermann
Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany/ NeuroCure Clinical Research Center, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

Frederike C Oertel
Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany/ NeuroCure Clinical Research Center, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany/ Department of Neurology, University of California, San Francisco, San Francisco, CA, USA

Joseph Kuchling
Friedemann Paul
Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine and

Introduction

Visual system damage is common in multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD).[1–3] The resulting visual function loss is assessed by visual acuity, contrast sensitivity, and visual fields.[4] Structural neuro-axonal visual system damage can be quantified by retinal optical coherence tomography (OCT) and demyelination of the afferent visual pathway by visual evoked potentials (VEP).[5,6]

An alternative and intriguing concept for assessing visual system damage is the measurement of dynamic functions, such as motion perception.[7,8] Motion perception begins in the retina where the signal is transferred through the magnocellular cells past the lateral geniculate nucleus to the middle temporal visual area to be cortically processed.[9,10] Deficits in motion perception were previously described in patients with MS and optic neuritis (ON).[11] These could be relevant for visual difficulties in executing everyday tasks.[12]

There are competing concepts regarding the cause of motion perception deficits in MS and ON. Worse motion perception was associated with increased VEP latencies,

Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany/ NeuroCure Clinical Research Center, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany/ Department of Neurology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

Klemens Ruprecht
Department of Neurology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

Alexander Klistorner
Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW, Australia/ Save Sight Institute, The University of Sydney, Sydney, NSW, Australia

Alexander U Brandt
Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany/ NeuroCure Clinical Research Center, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany/Department of Neurology, University of California, Irvine, Irvine, CA, USA

and both persisted after recovery of static visual function following acute ON.[13] Impaired motion perception might thus be the clinical correlate to prolonged VEP or side-discrepant latencies reflecting optic nerve demyelination.[13] Based on these findings, studies in MS suggested motion perception as a marker for visual dysfunction and demyelination.[13,14] However, motion perception changes are not specific for ON and are also altered in primary open-angle glaucoma,[15] Alzheimer's disease[16] and in autism.[17] This suggests that motion perception deficits could originate from different levels of the visual system and involve higher cortical function. Especially cognitive deficits could be relevant confounders in MS, since patients regularly present with cognitive dysfunction and motion perception testing requires a certain ability of information processing.[18]

Thus, the aim of our study was (a) to confirm the association of motion perception with VEP-assessed visual pathway myelination status in MS, (b) to explore associations with structural retinal damage and cognition and (c) to first-time investigate motion perception in patients with NMOSD.

Materials and methods

Patient and controls

Inclusion criteria for this prospective, cross-sectional study were an age between 18 and 70 years and a diagnosis of relapsing-remitting multiple sclerosis (RRMS) according to the 2017 revised McDonald criteria,[1] clinically isolated syndrome (CIS), NMOSD according to the 2015 International Consensus Diagnostic Criteria[2] or – for healthy controls (HC) – being free of neurological diseases. Exclusion criteria were any comorbidities influencing vision or the retina. Patients and HC were recruited from ongoing prospective observational cohort studies at Charité – Universitätsmedizin Berlin and at Macquarie University, Sydney. Berlin patients were clinically assessed and scored using the Expanded Disability Status Scale (EDSS)[19] and underwent the Symbol Digit Modalities Test (SDMT), a test for information processing speed and concentration.[20]

This study was approved by the local ethics committees in Berlin and Sydney and conducted in accordance with the Declaration of Helsinki in its applicable version and applicable local laws. All participants gave written informed consent.

Motion perception

Motion perception, specifically numbers from motion (NFM), was tested monocularly under habitual visual acuity (personal eye ware, if applicable) on a computer screen at a distance of 50 cm, using a revised testing software developed by the Functional Magnetic Resonance Imaging (fMRI) Unit, Neurology Department, Hadassah.[7] The test presents moving pixels revealing camouflaged three-digit numbers, based on the motion perception test assessed by Regan et al.[11] and is programmed to output an automatically calculated score ranging from 0 (worst) to 140 (best).[7] Prior to the test, all subjects underwent a short binocular training session. In two ON eyes of two MS patients and one NMOSD eye, NFM assessment was not possible due to low visual function. Those eyes were excluded from all analyses.

Visual function

In Berlin, high contrast VA (HCVA) and low contrast letter acuity (LCLA) were acquired monocularly with best refraction correction. HCVA was assessed by the use of retro-illuminated ETDRS charts in 4 m distance and converted into logMAR units. LCLA was tested with 2.5% contrast retro-illuminated Sloan charts in 2 m distance. As reported by a recent study, the use of the motion tool might be limited in patients with low VA, therefore a supplementary analysis of a subgroup including only patients with HCVA $\leq$ 0.1 logMAR was performed.[21] For this analysis, one eye with lower HCVA from the main MS cohort and three eyes from the NMOSD cohort were excluded.

In Berlin, full-field VEP was measured under best refraction correction using the RETI-port/scan 21 device (Roland Consult GmbH, Brandenburg, Germany) with gold-cup electrodes and the DantecTM Keypoint VEP system (Natus Europe GmbH, Planegg, Germany).[8] We analysed measurements of the different VEP devices separately and had to exclude MS and NMOSD patients' VEP measurements from 5 eyes due to insufficient VEP signal. We therefore analysed a subset of 47 eyes of 24 MS patients and 23 eyes of 12 NMOSD patients measured on the first device and a subset of 23 eyes of 12 MS (ON/NON eyes: 4/19) patients measured on the second device.

In Sydney, multifocal VEP (mfVEP) were tested under best corrected conditions using the VisionSearch 1 system (VisionSearch, Sydney, NSW, Australia) with four gold-disc electrodes (Grass, West Warwick, RI, US).[22] The mean mfVEP latency of the 56 segments was used for statistical analysis.

Optical coherence tomography

All participants underwent retinal examination using a spectral domain OCT (Spectralis SD-OCT; Heidelberg

Table 1. Demographic and clinical cohort description.

		Berlin Cohort			Sydney Cohort
		MS	NMOSD	HC	MS
Participants	$N_{patients}$	38	13	33	43
Sex	Male/female ($N_{patients}$)	11/27	1/12	9/24	16/27
Age/years	Mean ± SD (range)	36.56 ± 9.95 (20–61)	47.86 ± 15.36** (21–66)	37.37 ± 15.85 (21–70)	42.72 ± 10.02 (19–65)
None/Unilateral/ Bilateral ON	$N_{patients}$	16/18/4	6/1/6		19/24/0
Eyes with previous ON	yes/no (N_{eyes})	22/54	13/12		31/55
Time from last ON/years	Mean ± SD (range)	5.56 ± 8.51 (0.08–28.75)	5.88 ± 3.64 (1.17–12.92)		
Disease duration/years	Mean ± SD (range)	3.46 ± 3.61 (0.08–17.67)	5.67 ± 3.33 (0.33–12.75)		
EDSS	Median (range)	1.5 (0–4.5)	3.5 (1.5–6.0)		
SDMT	Mean ± SD (range)	63.42 ± 13.65 (34–94) (n = 33)	51.15 ± 4.12 (45–57) (n = 13)		

MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorders; HC: healthy controls; SD: standard deviation; ON: optic neuritis; EDSS: expanded disability status scale; SDMT: symbol digit modalities test.
Significant difference to HC marked by asterisks: *p = 0.05, **$p \leq 0.01$, ***$p \leq 0.001$.

Engineering, Heidelberg, Germany). We acquired a ring scan for peripapillary retinal nerve fibre layer thickness (pRNFL) and a 6 mm diameter macular volume scan for combined ganglion cell and inner plexiform layer (GCIP) and inner nuclear layer (INL) volume. Detailed OCT methods–in line with the APOSTEL recommendations[23] and including segmentation[8,24] and quality control[25] can be found elsewhere. Eight scans from seven subjects had to be excluded due to insufficient quality.

Statistical analysis

Statistical analyses were performed with R version 3.4.2 including geepack package 1.2-1 and ggplot2 version 3.1.0.[26] All results are given as mean ± standard deviation (SD), unless indicated differently. Generalized estimating equation (GEE) models with working correlation matrix 'exchangeable' and corrected for age were used for associations involving eye-related measurements accounting for within-subject inter-eye effects and for group comparisons. GEE results are given with regression coefficient (B) and standard error (SE). Linear regression models including each eye as an individual case were applied when including only one eye per subject. Statistical significance was established at $p < 0.05$. Due to the exploratory nature of the study, no correction for multiple testing was performed.

Data availability

The datasets for this manuscript will be shared by request from any qualified investigator.

Results

In Berlin, 33 patients with RRMS, 5 patients with CIS (of those, 2 with unilateral ON and 3 with other symptoms), 13 patients with NMOSD (Anti-Aquaporin 4 antibody +/−: 11/2), and 33 HC were included. Patients with RRMS and CIS were pooled and referred to as 'MS'. One eye of a MS patient was excluded due to amblyopia, and one eye of a NMOSD patient was excluded due to a branch retinal artery occlusion. A demographic and clinical overview is given in Table 1, exclusions are shown in Figure 1. From Sydney, 43 RRMS patients (male/female (n) = 16/27, mean age (years) ± SD = 42.36 ± 9.03, 24 with a unilateral ON history) were included. Main results from both centres are shown in Table 2.

Motion perception in healthy controls

The mean NFM score in HC was 126.6 ± 12.3 and did not differ between female and male HCs (126.5 ± 12.4 vs 127.1 ± 12.4, $B = -2.75$, SE = 4.32, p = 0.524) (Figure 2(a)). Lower NFM scores were associated with older age ($B = -0.698$, SE = 0.171, $p <$ 0.001; Figure 2(b)) in HC.

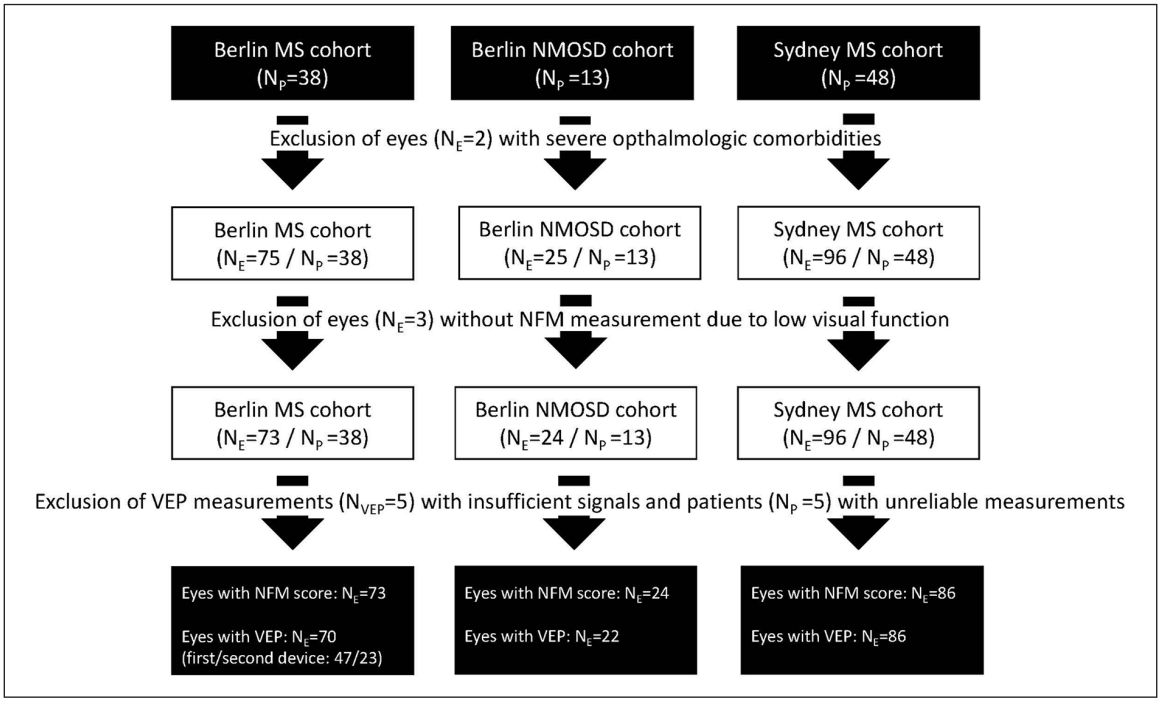

Figure 1. Exclusion flow chart for the Berlin MS/NMOSD and the Sydney MS cohorts.
Flow chart showing the exclusions in the three main cohorts in this study.
MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorders; N_P: number of patients; N_E: number of eyes; N_{VEP}: number of VEP measurements.

Motion perception in multiple sclerosis

MS patients in the Berlin cohort had an NFM score of 114.8 ± 23.2, which was lower than in HC (B = −12.374, SE = 3.285, $p < 0.001$). NFM scores did not differ between ON and non-ON eyes (B = −7.965, SE = 5.823, p = 0.171). Further, NFM was associated with HCVA (B = −139.4, SE = 29.7, $p < 0.001$), LCLA (B = 0.99, SE = 0.32, p = 0.002), pRNFL (B = 1.0, SE = 0.2, $p < 0.001$) and GCIP (B = 64.8, SE = 14.3, $p < 0.001$) (Figure 3(a)–(d)). In contrast, INL (B = −64.4, SE = 43.0, p = 0.152, Figure 3(e)) and P100 latency (B = −0.4, SE = 0.5, p = 0.400, Figure 3(f)) were not associated with NFM score. In a subset with no missing VEP measurements of the first device, associations of pRNFL and GCIP with NFM were still significant. Similar results were obtained when excluding the eye with HCVA > 0.1 logMAR.

In an analysis including only ON eyes (in case of ON in both eyes, only the eye with worse NFM was included), NFM score was associated with pRNFL (B = 1.464, SE = 0.349, r^2 = 0.545, $p < 0.001$, n = 18 eyes) and GCIP (B = 139.739, SE = 34.554, r^2 = 0.544, p = 0.001, n = 17 eyes) but not with P100 latency (B = −0.846, SE = 0.803, r^2 = 0.114 p = 0.317, n = 13 eyes). When performing asymmetry analysis in patients with unilateral ON, inter-eye NFM score was associated with inter-eye pRNFL (B = −1. 149, SE = 0.260, r^2 = 0.610, $p < 0.001$, n = 16), inter-eye GCIP (B = −77.588, SE = 15.362, r^2 = 0.688, $p < 0.001$, n = 15) but not with inter-eye P100 latency (B = −0.227, SE = 0.706, r^2 = 0.027, p = 0.756, n = 11). NFM was not associated with EDSS (B = 2.147, SE = 2.488, p = 0.390), but with SDMT score (B = 0.396, SE = 0.188, p = 0.035). After the exclusion of one eye with a recent ON episode (27 days before the visit) similar results were obtained, except for the association of NFM with SDMT (B = 0.221, SE = 0.197, p = 0.260). Similar results were also obtained after excluding the outliers with a NFM below 50 (Supplemental Figure 1). In a separate analysis of the VEP measurements from the second device, we found no association between NFM and P100 latency (B = 0.497, SE = 0.894, p = 0.580), excluding one eye with HCVA > 0.1 logMAR (Supplemental Figure 2).

In the Sydney cohort, a lower NFM score was likewise associated with thinner pRNFL (B = 1.351, SE = 0.276, $p < 0.001$). In contrast to the Berlin MS cohort, NFM score in the Sydney cohort was significantly lower in ON (92.92 ± 41.21) than in non-ON eyes (113.74 ± 20.77, B = −24. 955, SE = 6.911, $p < 0.001$) and was inversely associated with mfVEP latencies (B = −1.159, SE = 0.296, $p < 0.001$). In a multivariable analysis (NFM~pRNFL + P100) the

Table 2. Mean results of Numbers from motion score and all functional and structural visual parameters for eyes with optic neuritis and without optic neuritis in MS, NMOSD patients and for healthy controls.

		Berlin Cohort				Sydney cohort	
		MS ONeyes	MS NONeyes	NMOSD ONeyes	NMOSD NONeyes	MS ONeyes	MS NONeyes
NFM	Score	110.45 ± 29.58* (n = 20)	116.49 ± 20.42*** (n = 53)	80.71 ± 47.45*** (n = 12)	110.50 ± 18.23* (n = 12)	92.92 ± 41.21*** (n = 24)	113.74 ± 20.77** (n = 62)
HCVA	LogMAR units (Mean ± SD)	−0.03 ± 0.35 (n = 20)	−0.15 ± 0.08 (n = 52)	0.22 ± 0.56 (n = 12)	−0.10 ± 0.11 (n = 12)		
LCLA	Letters (out of 70) (Mean ± SD)	34.85 ± 14.78 (n = 20)	45.38 ± 5.69 (n = 52)	30.33 ± 12.29 (n = 9)	38.58 ± 9.72 (n = 12)		
VEP	P100 latency (Mean ± SD)	116.75 ± 13.25 (n = 15)	109.19 ± 8.06 (n = 32)	119.14 ± 12.75 (n = 10)	114.33 ± 9.13 (n = 12)		
mfVEP	Latency (Mean ± SD)					162.58 ± 15.43 (n = 24)	153.56 ± 12.36 (n = 62)
pRNFL	Thickness in µm (Mean ± SD)	83.80 ± 15.10 (n = 20)	97.20 ± 9.47 (n = 53)	67.50 ± 23.55 (n = 12)	96.83 ± 13.62 (n = 12)	76.33 ± 11.77 (n = 24)	90.21 ± 11.25 (n = 62)
GCIP	Volume in mm^3 (Mean ± SD)	1.67 ± 0.16 (n = 19)	1.93 ± 0.15 (n = 52)	1.54 ± 0.29 (n = 12)	1.95 ± 0.19 (n = 12)		
INL	Volume in mm^3 (Mean ± SD)	1.04 ± 0.07 (n = 19)	1.02 ± 0.06 (n = 52)	0.98 ± 0.10 (n = 12)	0.98 ± 0.08 (n = 12)		

MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorders; (N)ON: (non-) optic neuritis; n: number of eyes; HC: healthy control; HCVA: high contrast visual acuity; LCLA: low contrast letter acuity; VEP: full field visual evoked potentials; mfVEP: multifocal visual evoked potentials; pRNFL: peripapillary retinal nerve fibre layer; GCIP: ganglion cell/inner plexiform layer; INL: inner nuclear layer.
Significant difference to HC marked by asterisks: *$p = 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ (only analysed for NFM).

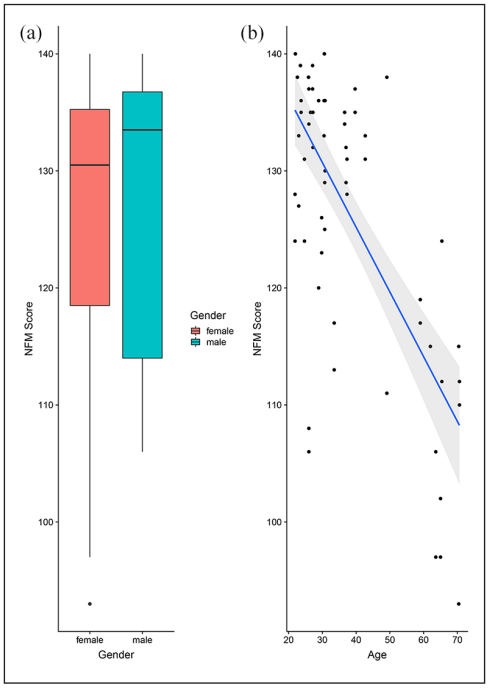

Figure 2. Numbers from motion score in healthy controls (a) boxplots comparing the numbers from motion (NFM) scores between female and male, healthy controls and (b) scatterplot showing the association of NFM scores measurements with age in healthy controls.

influence of pRNFL on NFM ($B = 0.987$, SE = 0.293, $p < 0.001$) was more pronounced than of mfVEP latencies ($B = -0.533$, SE = 0.309, $p = 0.085$). When only ON eyes were analysed, the association between NFM and pRNFL ($B = 2.120$, SE = 0.594, $r^2 = 0.367$, $p = 0.002$) was found to be stronger than between NFM and mfVEP latencies ($B = -1.097$, SE = 0.531, $r^2 = 0.187$, $p = 0.051$). Asymmetry analysis in unilateral ON patients demonstrated a significant association of decreased NFM in ON eyes with thinner pRNFL ($B = -1.409$, SE = 0.532, $r^2 = 0.242$, $p = 0.015$), but only a trend towards an association with longer mfVEP latency ($B = -1.128$, SE = 0.572, $r^2 = 0.150$, $p = 0.062$). Similar results were obtained after excluding the outliers with a NFM below 20 (Supplemental Figure 3).

Motion perception in neuromyelitis optica spectrum disorders

NFM score in patients with NMOSD was 91.1 ± 39.6 and lower than in HC ($B = -34.5$, SE = 10.4, $p < 0.001$). NFM score was lower in ON eyes than in non-ON eyes (Table 2, $B = -30.9$, SE = 15.1, $p = 0.041$) and NFM score in non-ON eyes was still lower than in HC ($B = -21.04$, SE = 5.9, $p < 0.001$). There was an association between NFM score and HCVA ($B = -77.2$, SE = 5.2, $p < 0.001$), LCLA ($B = 1.6$, SE = 0.3, $p < 0.001$), pRNFL ($B = 0.92$, SE = 0.38, $p = 0.016$) and GCIP ($B = 79.5$, SE = 28.7, $p = 0.006$) (Figure 4(a)–(d)). INL ($B = -55.4$, SE = 63.5, $p = 0.383$) and P100 latency ($B = -0.786$, SE = 0.713, $p = 0.270$) were not associated with NFM score (Figure 4(e) and (f)). NFM was neither associated with EDSS ($B = 0.819$, SE = 3.502, $p = 0.815$) nor with SDMT score ($B = 0.355$, SE = 0.593, $p = 0.550$). When excluding the eyes with HCVA > 0.1 logMAR (3 eyes from 2 patients) similar results were obtained but for the association between NFM and pRNFL ($B = 0.360$, SE = 0.284, $p = 0.205$). When excluding the outliers with a NFM score of 0 the influence of pRNFL ($B = 0.293$, SE = 0.157, $p = 0.062$ on NFM was, though not significantly, still more pronounced than of P100 latencies ($B = 0.008$, SE = 0.286, $p = 0.977$). Trends towards the previous associations remained (Supplemental Figure 4).

Discussion

The results of this study (a) support an association of motion perception with VEP-assessed visual pathway myelination status in MS, (b) reveal impaired motion perception in NMOSD, (c) demonstrate association of motion perception with neuro-axonal visual system damage and reduced HCVA, and (d) suggests that motion perception is associated with cognitive deficits in MS but not NMOSD.

In earlier studies on early-stage MS and acute cases of ON, impaired motion perception was associated with longer VEP latencies in ON eyes.[7,13] Therefore motion perception, as a dynamic visual function, was hypothesized to rely on a rapid transmission of visual information reflecting myelination levels of the visual pathway.[13]

In our study both cohorts demonstrated a strong association between NFM score and pRNFL and GCIP loss, suggesting that neuro-axonal damage of the retina and optic nerve is one of the main drivers behind reduced motion perception in autoimmune inflammatory optic neuropathies.

While our study demonstrated no association between motion perception and VEP latencies from the main and second device in the Berlin cohort, the Sydney cohort found correlations of lower NFM score with mfVEP latency delay in its entire cohort and in ON eyes specifically. This may be explained by the larger sample size and multifocal mfVEP used in Sydney, which is more sensitive to demyelination damage than typical full-field VEP,[3] as well as by more pronounced neuro-axonal damage in terms of pRNFL thickness in

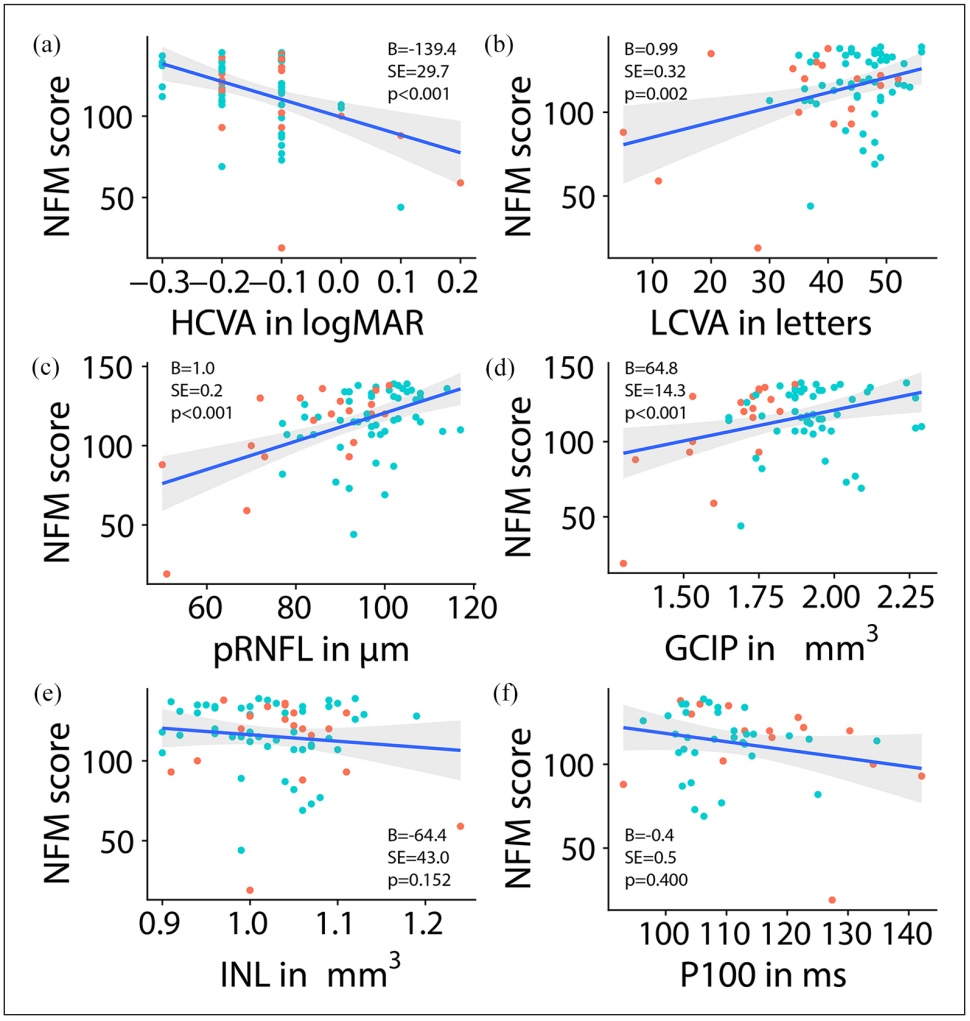

Figure 3. Association of numbers from motion (NFM) scores with functional and structural visual parameters in the main multiple sclerosis cohort (a) high contrast visual acuity (HCVA), (b) low contrast letter acuity (LCLA), (c) peripapillary retinal nerve fibre layer (pRNFL) thickness, (d) ganglion cell/inner plexiform layer (GCIP) volume; (e) INL: inner nuclear layer (INL) volume and (f) P100 latency; Red points represent optic neuritis eyes, turquoise points non-optic neuritis eyes.

ON eyes of the Sydney cohort compared to the Berlin cohort. Furthermore, the mean P100 latency being only slightly delayed in the Berlin cohort, one could hypothesize whether motion perception is only affected by severely delayed latencies. A future analysis of binocular motion perception testing in unilateral ON patients might yield clarification.

Weaker correlation between NFM score and VEP latencies (in comparison to pRNFL) is also apparent in the asymmetry analysis of patients with unilateral ON history, which is less susceptible to high inter-individual range of measurements. Thus, while ON-related neuro-axonal damage, as represented by inter-eye pRNFL and GCIP thinning, is associated with inter-eye motion perception impairment, it does not correlate with full-field VEP latency of the main cohort and only shows trend in the confirmatory cohort. These findings indicate that prolonged visual input transmission is not the only driver of impaired motion perception in our cohorts. Thus, we suggest an additional underlying pathophysiological process:

The processing of motion perception is considered to begin in the retina.[27] Previous studies found that a retinal circuit based on direction selective cells is at the origin of retinal motion encoding.[28–30] This circuit is focused around the interaction of various subtypes of bipolar, amacrine and ganglion cells, especially motion sensitive parasol ganglion cells.[31] The neurites of these cells stratify in the inner plexiform layer.[29] Our study showed that impaired motion perception

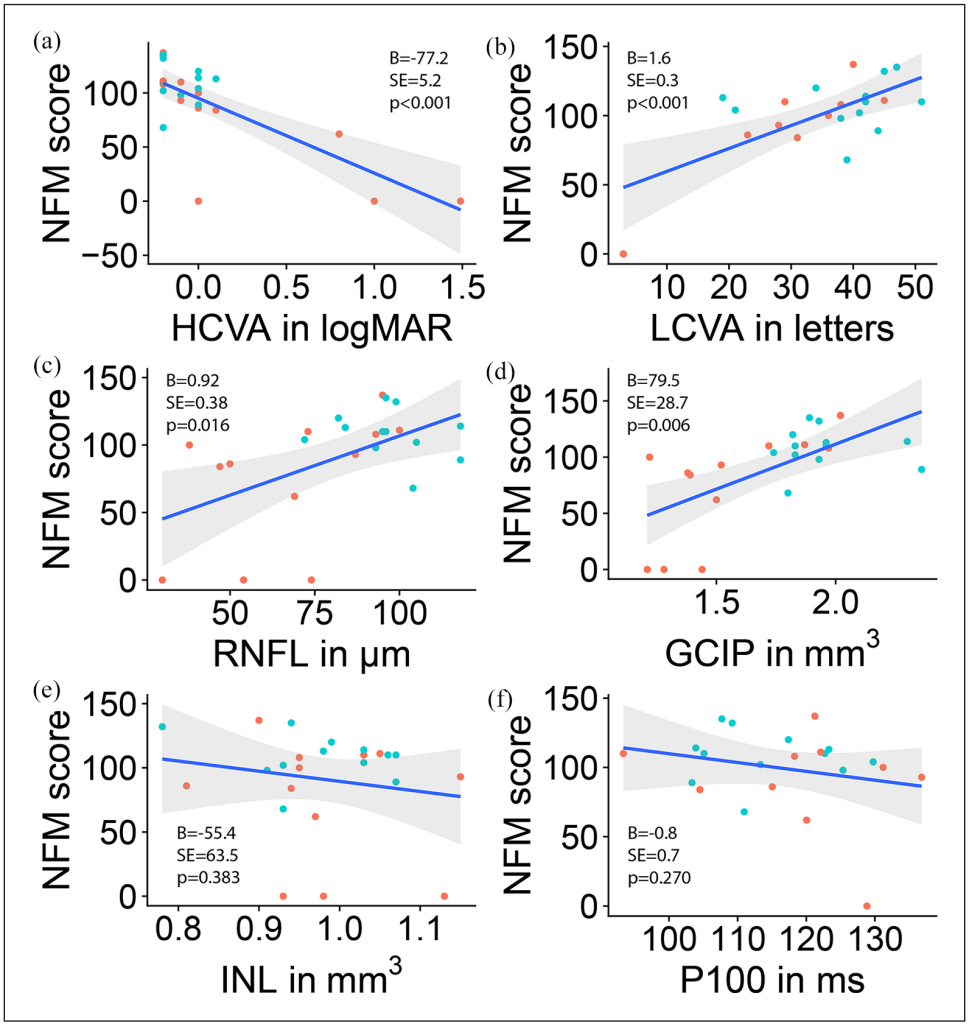

Figure 4. Association of NFM scores with functional and structural visual parameters in the neuromyelitis optica spectrum disorders cohort (a) high contrast visual acuity (HCVA), (b) low contrast letter acuity (LCLA), (c) peripapillary retinal nerve fibre layer (pRNFL) thickness, (d) ganglion cell/inner plexiform layer (GCIP) volume; (e) INL: inner nuclear layer (INL) volume (f) P100 latency; Red points represent optic neuritis eyes, turquoise points non-optic neuritis eyes.

was associated with pRNFL and GCIP thinning. GCIP and pRNFL thinning was shown to occur in MS and NMOSD patients with and without prior ON.[5,6,32] Therefore, we suggest that motion perception relies on the structural integrity of the retina and represents a clinical correlate of neuro-axonal damage. The fact that we reproduced the association of motion perception impairment with pRNFL and GCIP thinning in NMOSD supports this idea, as the effect of axonal loss was shown to be stronger in NMOSD than in MS.[6,22] This concept would also explain motion perception impairment in non-demyelinating diseases such as glaucoma, which features RNFL and GCIP damage as a consequence of increased intraocular pressure.[15,33] Motion perception impairment in Alzheimer's disease, however, might be caused by magnocellular pathway damage in the primary visual cortex.[16] In this context, it would be interesting to investigate an association of cortical damage with worsened motion perception in MS and NMOSD.

Our study is – to the best of our knowledge – the first describing motion perception in NMOSD. A recent study demonstrated different patterns of ON damage in MS and NMOSD, showing that ON damage in MS, while being less severe, might primarily be caused by demyelination, whereas in NMOSD, ON damage was more severe and axonal loss presented itself as the main pathological factor.[22] Motion perception in NMOSD was markedly reduced in comparison to controls, and more severely impaired in ON than in non-ON eyes, which could be explained by the strong ON-related

neuro-axonal damage in NMOSD. Notably, even in NMOSD non-ON eyes, motion perception was worse compared with controls, even in a similar range as MS ON eyes. This suggests a role of microstructural visual system changes for motion perception.[34] However, also the higher age in the NMOSD cohort might account for the lower NFM scores.

As also MS non-ON eyes showed decreased NFM in comparison to controls, motion perception impairment might occur attack-independent, reflecting chronic neurodegeneration in MS.

Motion perception in our study was also associated with HCVA and LCLA. Visual loss is associated with pRNFL and GCIP thinning.[5] It can therefore be questioned whether visual loss directly impairs motion perception. Motion perception testing was suggested to rely on normal VA. We therefore performed a subgroup analysis on patients with best-corrected HCVA $\leq$ 0.1 logMAR. The results did not differ from the initial results in our Berlin MS cohort.

However, the cohort differences between our study and the previous studies of motion perception in MS must also be taken into consideration. While our cohorts represented a heterogeneous group of MS patients in a stable phase of the disease, previous studies of motion perception in MS focused on patients with either early-stage MS, acute ON or progressive MS. In early-stage MS and acute ON, acute inflammation plays a crucial role, therefore results could be influenced by stronger effects of acute demyelination. Of note, VEP/mfVEP latencies of ON eyes in both our MS cohorts were only to a small degree prolonged in comparison to non-ON eyes (Table 2), indicating only subtle ON-related visual pathway demyelination and/or subclinical demyelination in the non-ON eyes.

Furthermore, most studies on motion perception in MS used OCT measurements only for cohort characterization, therefore missing the opportunity to study whether motion perception was affected by neuro-axonal damage.[14] One recent study featuring progressive MS patients showed no association between motion perception and OCT measurements,[21] although motion perception impairment in non-ON eyes of progressive MS was thought to possibly rely on axonal loss.[21] This finding could be explained with a different statistical approach.

We also show that motion perception was associated with SDMT, a commonly used test for measuring information processing speed and cognition in MS.[20] The motion tool used in our study relied on numbers being recognized, the task being directly associated with cognitive capacities is possible. Alternatively, SDMT score may be directly influenced by demyelination and thus reduced information processing speed in the afferent visual system.[35] This finding is however limited by a small sample size. Nevertheless, cognitive impairment does not seem to be a driver for motion perception impairment in our NMOSD cohort.

In MS, eye movement disorders, especially delayed saccadic latency, due to damage along the pathways of the visual system are observed and shown to be associated with impaired visual functioning in daily life.[36] Our motion perception test being based on fast moving pixels, delayed saccades might contribute to its impairment.

In healthy controls we found motion perception to be associated with age. This is in accordance with a study that reported motion perception to be impaired in older people due to a deficit in contrast sensitivity.[37]

This study is subject to limitations. The small sample size, especially for our NMOSD subgroup, might lead to subtle effects being overlooked, or significant effects could be overinterpreted. In fact, we were not able to reproduce all results when we excluded outliers. Due to the small sample size in our NMOSD subgroup, we chose not to exclude two patients with negative anti-aquaporin 4 antibodies. In our main cohort, VEP measurements of the main device were only available for a smaller subset of patients, and the subset of patients with VEP measurements of the second device had mostly no history of ON, which could explain why the association of motion perception to P100 latencies missed significance in this these groups. Motion perception testing was performed under habitual VA and uncorrected refraction errors might have influenced the results. As we performed a cross-sectional study, we cannot report on the development of motion perception over time. Furthermore, the heterogeneity of our main cohort regarding disease stages, especially with regards to the time since ON, might complicate the comparison to previous studies.

To conclude, our study suggests that motion perception impairment is likely to be a result of both visual pathway neuro-axonal damage and demyelination in MS and NMOSD. In the light of the past and current effort to study the neural circuits of motion processing, early motion encoding in the retina was found to play an important role. Motion perception impairment in MS and NMOSD might therefore present itself as a suitable human model for further investigations.

Acknowledgements

We thank Charlotte Bereuter and Jana Schließeit for excellent technical assistance, and Netta Levin and Yael Backner for providing the motion perception test software.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: FCO was employee of Nocturne GmbH, unrelated to this work. SA received a travel grant from Celgene and speaker's honorary from Alexion, Bayer and Roche. JBS has received travel grants and speaking honoraria from Bayer Healthcare, Biogen Idec, Merck Serono, Sanofi Genzyme, Teva Pharmaceuticals, Roche, and Novartis, none of them related to preparing this manuscript. KR received research support from Novartis, Merck Serono, German Ministry of Education and Research, European Union (821283-2), Stiftung Charité (BIH Clinical Fellow Programme) and Arthur Arnstein Foundation; received speaker honoraria and travel grants from Bayer, Biogen Idec, Merck Serono, sanofi-aventis/Genzyme, Teva, Roche, Novartis, and Guthy Jackson Charitable Foundation. FP serves as an Associate Editor for *Neurology: Neuroimmunology & Neuroinflammation*, reports research grants and speaker honoraria from Bayer, Teva, Genzyme, Merck, Novartis, MedImmune and is member of the steering committee of the OCTIMS study (Novartis). AUB is cofounder and shareholder of motognosis and nocturne. He is named as inventor on several patent applications regarding MS serum biomarkers, OCT image analysis and perceprive visual computing. HGZ received research grants from Novartis and speaking honoraria from Bayer Healthcare. All other authors declare that they have no conflicts of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Noah Ayadi https://orcid.org/0000-0002-3495-3825
Susanna Asseyer https://orcid.org/0000-0001-6289-1791
Alexander U Brandt https://orcid.org/0000-0002-9768-014X

Supplemental material

Supplemental material for this article is available online.

References

1. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173.
2. Wingerchuk DM, Banwell BL, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015; 85: 177–189.
3. Graham SL and Klistorner A. Afferent visual pathways in multiple sclerosis: A review. *Clin Exp Ophthalmol* 2017; 45(1): 62–72.
4. Petzold A, Wattjes MP, Costello F, et al. The investigation of acute optic neuritis: A review and proposed protocol. *Nat Rev Neurol* 2014; 10(8): 447–458.
5. Brandt AU, Martinez-Lapiscina EH, Nolan R, et al. Monitoring the course of MS with optical coherence tomography. *Curr Treat Options Neurol* 2017; 19(4): 15.
6. Oertel FC, Zimmermann H, Paul F, et al. Optical coherence tomography in neuromyelitis optica spectrum disorders: Potential advantages for individualized monitoring of progression and therapy. *EPMA J* 2018; 9(1): 21–33.
7. Raz N, Shear-Yashuv G, Backner Y, et al. Temporal aspects of visual perception in demyelinative diseases. *J Neurol Sci* 2015; 357: 235–239.
8. Ayadi N, Dörr J, Motamedi S, et al. Temporal visual resolution and disease severity in MS. *Neurol Neuroimmunol Neuroinflamm* 2018; 5: e492.
9. Born RT and Bradley DC. Structure and function of visual area MT. *Annu Rev Neurosci* 2005; 28: 157–189.
10. Chapman C, Hoag R and Giaschi D. The effect of disrupting the human magnocellular pathway on global motion perception. *Vision Res* 2004; 44(22): 2551–2557.
11. Regan D, Kothe AC and Sharpe JA. Recognition of motion-defined shapes in patients with multiple sclerosis and optic neuritis. *Brain* 1991; 114(pt 3): 1129–1155.
12. Frisen L, Hoyt WF, Bird AC, et al. Diagnostic uses of the Pulfrich phenomenon. *Lancet* 1973; 2: 385–386.
13. Raz N, Dotan S, Chokron S, et al. Demyelination affects temporal aspects of perception: An optic neuritis study. *Ann Neurol* 2012; 71(4): 531–538.
14. Raz N, Dotan S, Benoliel T, et al. Sustained motion perception deficit following optic neuritis: Behavioral and cortical evidence. *Neurology* 2011; 76: 2103–2111.
15. Silverman SE, Trick GL and Hart WM Jr. Motion perception is abnormal in primary open-angle

glaucoma and ocular hypertension. *Invest Ophthalmol Vis Sci* 1990; 31(4): 722–729.

16. Gilmore GC, Wenk HE, Naylor LA, et al. Motion perception and Alzheimer's disease. *J Gerontol* 1994; 49: P52–P57.
17. Bertone A, Mottron L, Jelenic P, et al. Motion perception in autism: A 'complex' issue. *J Cogn Neurosci* 2003; 15: 218–225.
18. Paul F. Pathology and MRI: Exploring cognitive impairment in MS. *Acta Neurol Scand* 2016; 134(suppl. 200): 24–33.
19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology* 1983; 33(11): 1444–1452.
20. Parmenter BA, Weinstock-Guttman B, Garg N, et al. Screening for cognitive impairment in multiple sclerosis using the Symbol digit Modalities Test. *Mult Scler* 2007; 13(1): 52–57.
21. Backner Y, Petrou P, Glick-Shames H, et al. Vision and vision-related measures in progressive multiple sclerosis. *Front Neurol* 2019; 10: 455.
22. Shen T, You Y, Arunachalam S, et al. Differing structural and functional patterns of optic nerve damage in multiple sclerosis and neuromyelitis optica spectrum disorder. *Ophthalmology* 2019; 126(3): 445–453.
23. Cruz-Herranz A, Balk LJ, Oberwahrenbrock T, et al. The APOSTEL recommendations for reporting quantitative optical coherence tomography studies. *Neurology* 2016; 86: 2303–2309.
24. Motamedi S, Gawlik K, Ayadi N, et al. Normative data and minimally detectable change for inner retinal layer thicknesses using a semi-automated OCT image segmentation pipeline. *Front Neurol* 2019; 10: 1117.
25. Tewarie P, Balk L, Costello F, et al. The OSCAR-IB consensus criteria for retinal OCT quality assessment. *PLoS One* 2012; 7(4): e34823.
26. R Core Team. R: A language and environment for statistical computing, 2017, https://www.R-project.org/
27. Barlow HB, Hill RM and Levick WR. Retinal ganglion cells responding selectively to direction and speed of image motion in the rabbit. *J Physiol* 1964; 173: 377–407.
28. Euler T, Detwiler PB and Denk W. Directionally selective calcium signals in dendrites of starburst amacrine cells. *Nature* 2002; 418: 845–852.
29. Kim JS, Greene MJ, Zlateski A, et al. Space–time wiring specificity supports direction selectivity in the retina. *Nature* 2014; 509: 331–336.
30. Matsumoto A, Briggman KL and Yonehara K. Spatiotemporally asymmetric excitation supports mammalian retinal motion sensitivity. *Curr Biol* 2019; 29: 3277.e5–3288.e5.
31. Manookin MB, Patterson SS and Linehan CM. Neural mechanisms mediating motion sensitivity in parasol ganglion cells of the primate retina. *Neuron* 2018; 97: 1327.e4–1340.e4.
32. Oertel FC, Specovius S, Zimmermann HG, et al. Retinal optical coherence tomography in neuromyelitis optica. *Neurol Neuroimmunol Neuroinflamm*, 8: e1068.
33. Weinreb RN, Aung T and Medeiros FA. The pathophysiology and treatment of glaucoma: A review. *JAMA* 2014; 311: 1901–1911.
34. Oertel FC, Kuchling J, Zimmermann HG, et al. Microstructural visual system changes in AQP4-antibody–Seropositive NMOSD. *Neurol Neuroimmunol Neuroinflamm* 2017; 4: e334.
35. Gabilondo I, Rilo O, Ojeda N, et al. The influence of posterior visual pathway damage on visual information processing speed in multiple sclerosis. *Mult Scler* 2017; 23(9): 1276–1288.
36. Nij Bijvank JA, Petzold A, Coric D, et al. Saccadic delay in multiple sclerosis: A quantitative description. *Vision Res* 2020; 168: 33–41.
37. Allen HA, Hutchinson CV, Ledgeway T, et al. The role of contrast sensitivity in global motion processing deficits in the elderly. *J Vis* 2010; 10: 15.