Published in final edited form as:

Curr Eye Res. 2018 July ; 43(7): 941–948. doi:10.1080/02713683.2018.1459730.

Visual Pathway Measures are Associated with Neuropsychological Function in MS

James Nguyen, BS¹, Alissa Rothman, BS¹, Kathryn Fitzgerald, ScD¹, Anna Whetstone, BS¹, Stephanie Syc-Mazurek, MS¹, Jannelle Aquino, DO¹, Laura J. Balcer, MD, MSCE², Elliot M. Frohman, MD, PhD³, Theresa Frohman, PA-C³, Ciprian Crainiceanu, PhD⁴, Meghan Beier, MA, PhD⁵, Scott D. Newsome, DO¹, Peter A. Calabresi, MD¹, and Shiv Saidha, MBBCh, MD, MRCPI¹

¹Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD

²Department of Neurology, New York University Langone Medical Center, New York, NY

³Department of Neurology and Ophthalmology, University of Texas Southwestern, Dallas, TX

⁴Department of Biostatistics, Johns Hopkins University, Baltimore MD

⁵Department of Physical Medicine and Rehabilitation, Johns Hopkins University School of Medicine, Baltimore MD

Abstract

Purpose: To determine relationships between visual function and GCIP thickness, and neuropsychological measures in MS.

Methods: Ninety-five relapsing-remitting (RRMS) and thirty-six progressive MS patients underwent 100%-contrast visual acuity (VA), 2.5%- and 1.25%-contrast letter acuity (LA) testing, Cirrus-HD OCT, and neuropsychological assessments. Mixed effects regression models were used to assess relationships.

Results: Across the cohort, 1.25%-contrast LA was associated with Symbol Digit Modalities Test (SDMT; $\beta=2.17$, $p=0.005$), and Brief Visuospatial Memory Test Revised (BVM-T-R) Total Recall (TR) and Delayed Recall (DR) scores ($\beta=0.31$, $p<0.001$; $\beta=0.15$, $p=0.039$, respectively). 2.5%-contrast LA was associated with BVM-T-R TR scores ($\beta=0.27$, $p=0.006$). In the RRMS cohort, 1.25%-contrast LA was generally more significantly associated with cognitive measures; SDMT ($\beta=2.97$, $p=0.001$), BVM-T-R TR ($\beta=0.32$, $p<0.001$) and DR ($\beta=0.22$, $p=0.012$).

Conclusion: This study suggests that visual pathway measures, particularly visual function measures, reflect aspects of cognitive function in MS, further supporting their roles as complementary outcomes in MS neuroprotection trials.

Address reprint requests & correspondence to: Dr. Shiv Saidha, Associate Professor of Neurology, Division of Neuroimmunology and Neurological Infections, Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, MD 21287, USA, Tel: (410) 614-1522, Fax: 410-502-6736, ssaidha2@jhmi.edu.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the contents and writing of the paper. The following manuscript has not been published elsewhere and has not been submitted simultaneously for publication elsewhere.

Keywords

visual pathway; visual function; neuropsychological assessment; multiple sclerosis; optical coherence tomography

INTRODUCTION

Retinal neurodegeneration resulting from optic neuropathy in multiple sclerosis (MS) can be structurally quantified by optical coherence tomography (OCT), a high-resolution imaging technique that enables rapid, non-invasive quantification of retinal layers. OCT-derived ganglion cell + inner plexiform layer (GCIP) thickness correlates with global disability, as well as high- and, in particular, low-contrast visual function (emerging functional outcomes) in MS [1-3]. Furthermore, rates of GCIP atrophy are accelerated in active MS, and closely linked with rates of brain atrophy over time [1,4]. Therefore, GCIP thickness provides valuable insight regarding global neurodegeneration in MS.

Cognitive impairment is a highly relevant clinical feature of MS evident in 40-70% of patients [5]. The Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) battery of neuropsychological testing is established for assessing cognitive function in MS [6]. In addition, the Multiple Sclerosis Functional Composite (MSFC) assessment also partially assesses cognition with the Paced Auditory Serial Addition Test (PASAT), as well as dexterity and walking speed. While brain sub-structure volumes have been shown to correlate with cognitive function in MS, and despite the proposed utility of structural and functional visual pathway (VP) measures (complementary to MRI) in tracking MS patients clinically [7], as well as outcomes in clinical trials, few studies have comprehensively assessed the relationships between VP and neuropsychological measures in MS. Moreover, there have been conflicting results between studies performed. Peripapillary retinal nerve fiber layer (RNFL) thickness has been found to correlate with SDMT scores in some studies [8-10], and low-contrast letter acuity has been found to be associated with PASAT and SDMT scores [11,12]. However, with relatively small sample sizes, limited neuropsychological evaluation, and partial VP assessment (GCIP thickness, for example, has been shown to be a more superior OCT measure than RNFL thickness as it more greatly reflects global neurodegeneration in MS and is less susceptible to edema [1]), the relationships between VP measures and neuropsychological function in MS remain unclear.

Given the known relationship between GCIP thickness and brain volume in MS, we hypothesized that GCIP thickness would also partially reflect cognitive function in MS. However, since high, and in particular low-contrast visual function are also strongly associated with GCIP thickness, and attention and visual memory, among other cognitive functions are necessary to perform visual function testing, we hypothesized that visual function would more greatly reflect neuropsychological function than GCIP thickness in MS. Thus, in this cross-sectional study, we investigated the relationships between functional (high- and low-contrast visual function) as well as structural (OCT derived retinal layer and, in particular, GCIP thicknesses) VP measures and cognitive measures in MS, further

assessing the degree to which VP measures may reflect clinically relevant aspects of the MS disease process.

PATIENTS AND METHODS

Patients

MS patients were recruited by convenience sampling from the Johns Hopkins MS Center. All study protocols were approved by the Johns Hopkins University Institutional Review Board and written informed consent was obtained from all participants. MS diagnoses were based on the 2010 revised McDonald criteria [13]. Patients were categorized according to the Lublin classification as having either relapsing remitting (RRMS), secondary progressive (SPMS), or primary progressive MS (PPMS) [14]. Due to the relatively small SPMS and PPMS sample sizes, progressive participants were combined into one group designated progressive MS (PMS) for analytical purposes. MS patients attending our center are encouraged to attend an ophthalmologist for assessment annually as part of their routine standard of care. By medical history/chart review, we excluded participants with glaucoma, diabetes, uveitis, eye trauma or surgery, hypertension, refractive errors of greater than or equal to ± 6 diopters, a history of ON within 6 months of OCT acquisition, or other neurological or ophthalmological disorders. Disease duration, age, ethnicity, sex, years of education and history, date, and side of ON were recorded.

OCT

Spectral-domain Cirrus HD-OCT (model 5000, software version 6.0; Carl Zeiss Meditec, Dublin, California) was used to perform retinal imaging by experienced technicians. Peripapillary and macular images were obtained using the 200 $\times$ 200 optic disc and 512 $\times$ 128 macular cube protocols, respectively, as described in detail elsewhere [15]. In accordance with the OSCAR-IB criteria, which have been validated in MS [16], only scans with signal strength equal to or greater than 7/10 without artifact were included [17].

In addition, a highly reproducible OCT segmentation analysis was performed to compute GCIP, inner nuclear layer (INL), and outer nuclear layer (ONL) thicknesses, as previously described. This validated method has been shown to detect significant differences between healthy control and MS eyes [18].

Neuropsychological and visual function evaluation

To assess cognitive function, the MACFIMS battery of neuropsychological testing was administered according to standard protocols - Paced Auditory Serial Addition Test (PASAT), oral Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test Revised (BVM-T-R), Benton Judgment of Line Orientation (JLO), Delis-Kaplan Executive Function System (DKEFS), and Controlled Oral Word Association Test (COWAT) tests. In addition to the PASAT, 25-foot-walk and 9-hole-peg assessments were also performed in order to complete MSFC determinations. Moreover, the American National Adult Reading Test (AMNART) was also performed to estimate premorbid intelligence [19-24]. Furthermore, participants were also administered the Beck Depression Inventory-II (BDI) and Modified Fatigue Impact Scale (MFIS) in order to measure self-reported depressive

symptoms and impact of fatigue on physical, cognitive, and psychosocial function, respectively. Each cognitive test and survey performed as part of the study is outlined in Table 1.

Z-scores for MSFC, oral SDMT, BVM-T-R, COWAT, and DKEFS Sorting were computed using manual norms as described elsewhere [19-21, 24]. Briefly, z-scores for each individual MSFC sub-test (PASAT, 25-foot-walk, and 9-hole-peg-test) were averaged, forming a composite MSFC z-score. Oral SDMT raw scores were converted into z-scores, adjusting for age and level of education in years. BVM-T-R raw scores were converted into z-scores, adjusting for age. DKEFS Sorting raw scores were converted into scaled scores for each of the two tested conditions (free sorting and sort recognition). These individual scaled scores were averaged to form a composite DKEFS Sorting scaled score. Raw scores for JLO, AMNART, BDI, and MFIS were used in analyses.

High contrast (100%) Early Treatment Diabetic Retinopathy Study (ETDRS) and low-contrast (2.5% and 1.25%) Sloan letter charts (Precision Vision, Lasalle, IL) were administered at 4m and 2m respectively, with each eye scored separately. Participants used their habitual distance corrective lenses. Visual assessments were administered in a darkened room by trained technicians using standard testing protocols [3]. Scores were calculated based on the total number of letters patients read correctly (with each chart containing 5 letters/line across 14 lines; for a total possible score of 70 letters correctly identified).

All neuropsychological and visual function assessments were determined within 6 months of OCT scanning.

Statistical Analysis

Statistical analyses were performed using Stata (version 12; StataCorp LP, College Station, TX). Initial analyses compared MS subtypes with respect to demographic characteristics including age, sex, race and years of education, as well as disease history including duration and ON history. Comparisons between MS subtypes in regard to proportions of eyes with ON history and differences in sex were performed using the chi-square (χ^2) test. The Wilcoxon rank-sum test was used to assess differences in age and disease duration between sub-types. The Shapiro-Wilk test was used to assess normality of distributions. We then assessed the association between cognitive outcomes and visual pathway measurements using mixed-effects linear regression analyses to account for within-subject inter-eye correlations. We adjusted models for age, sex, disease duration, years of education, and ON history. We also calculated partial correlation coefficients, adjusting for age, sex, disease duration, years of education, and ON history in RRMS only as a descriptive measure to illustrate the capacity of VP measures to predict neurocognitive outcomes. The RRMS cohort was chosen for this purpose since RRMS constituted the majority of the study cohort. We did not correct for multiple comparisons as this study was hypothesis-driven [25]. We defined statistical significance as $p < 0.05$.

RESULTS

Clinical Findings

One hundred and thirty one patients (95 RRMS and 36 PMS) fulfilled eligibility criteria and participated in the study. Consistent with prior studies, mean age and disease duration were higher in PMS as compared to RRMS (both: $p < 0.001$; Table 2), with RRMS patients exhibiting a greater proportion of eyes with a history of ON (25%), as compared to PMS (13%; $p = 0.03$; none of the PPMS patients had a prior history of ON). No significant differences were found between the proportions of females or proportions of participants according to ethnicity classifications between RRMS and PMS. At time of OCT scanning, 47 RRMS (25%) and 9 PMS (13%) eyes had a known history of prior ON. Mean 100%-VA, 2.5%- and 1.25%-LA scores [3], mean GCIP thicknesses [7], and cognitive scores [26-27] observed in the current MS cohort are similar to those that have been previously reported in other MS cohorts (Table e-1). Seventeen right eyes and 21 left eyes in total were excluded from OCT analyses due to inadequate OCT quality. The summary of demographics and patient characteristics is outlined in Table 2.

Relationships between Low-contrast letter acuity (LCLA) and Cognition

All patients—We observed a significant association between 1.25%-contrast LA and BMVT-R total recall (TR) and delayed recall (DR) ($\beta = 0.31$, $p < 0.001$; $\beta = 0.15$, $p = 0.04$ respectively), as well as SDMT ($\beta = 2.17$; $p = 0.005$) scores. 2.5%-contrast LA was associated with BVMT-R TR ($\beta = 0.27$, $p = 0.006$) and trended towards being associated with SDMT scores ($\beta = 1.61$, $p = 0.09$) (Table 3).

Relapsing remitting cohort—In RRMS, somewhat more extensive relationships between LCLA and cognition were evident (Table 4). 1.25%-contrast LA was significantly associated with SDMT ($\beta = 2.97$, $p = 0.001$, $r = 0.34$), BVMT-R TR ($\beta = 0.32$, $p < 0.001$, $r = 0.43$) and DR ($\beta = 0.22$, $p = 0.012$, $r = 0.33$) scores (Figure 1). In addition, 2.5%-contrast LA was associated with Delis-Kaplan Executive Function System Sorting (DKEFS; $\beta = 2.46$, $p = 0.006$, $r = 0.41$) and BVMT-R TR scores ($\beta = 0.22$, $p = 0.049$, $r = 0.25$). We also noted a borderline association between 2.5%-contrast LA and SDMT scores ($\beta = 2.18$, $p = 0.07$, $r = 0.20$).

Progressive cohort—In PMS, there were fewer relationships between LCLA and cognition. 2.5%-contrast LA was significantly associated with MSFC scores ($\beta = 2.58$, $p = 0.005$) (Table e-2).

Relationships between high contrast VA (HCVA) and cognition

Overall, fewer relationships were observed between neuropsychological measures and HCVA scores, as compared to LCLA scores. We did note significant associations for HCVA with BVMT-R TR (Table 3; $\beta = 0.21$, $p = 0.002$) and DR scores ($\beta = 0.19$, $p = 0.006$) and marginal associations (which did not reach statistical significance) with SDMT ($\beta = 1.28$, $p = 0.09$) and MFIS ($\beta = 0.11$, $p = 0.069$) scores. Subgroup analyses revealed that HCVA was significantly associated with BVMT-R DR ($\beta = 0.23$, $p = 0.008$, $r = 0.30$) and JLO scores ($\beta = 0.54$, $p = 0.027$, $r = 0.26$) in RRMS, as well as BVMT-R TR scores in both RRMS ($\beta = 0.33$,

$p < 0.001$, $r = 0.39$) (Table 4) and PMS ($\beta = 0.29$, $p = 0.021$). In PMS, HCVA was also significantly associated with MSFC scores ($\beta = 2.30$, $p < 0.001$) (Table e-2).

Relationships between OCT parameters and cognition

In RRMS, there was a significant association between GCIP thickness and DKEFS-Sorting scores ($\beta = 1.61$, $p < 0.001$, $r = 0.60$) (Table 4). Additionally, average retinal thickness was associated with both BVMT-R DR $\beta = 0.25$, $p = 0.047$, $r = 0.26$) and DKEFS scores ($\beta = 2.44$, $p = 0.02$, $r = 0.45$), while trended towards significance with BVMT-R TR scores in RRMS (Table 4). We did not find associations between INL and ONL thicknesses and any neuropsychological outcomes.

DISCUSSION

The results of this study suggest that VP measures, particularly low-contrast visual function are broadly associated with diverse aspects of cognitive function in MS, providing further support that they are simultaneously affected in MS and provide insight regarding the global MS disease process. While VP measures, and in particular LCLA, were associated with neuropsychological measures reflecting information processing and memory (SDMT and BVMT-R, respectively) across the MS cohort, more extensive relationships between VP measures and neuropsychological measures including executive functioning, language and abstract thought (DKEFS and COWAT) were detected in the RRMS subtype. In PMS, HCVA and LCLA were associated with functional performance and visual learning (MSFC and BVMT-R, respectively).

These findings may be in accordance with prior studies, which suggest that not only may LCLA better capture visual dysfunction in MS than HCVA, but also that LCLA may be a more encompassing and reliable biomarker and outcome reflective of the MS disease process [28]. Additionally, our study findings support preliminary studies that found associations between LCLA and cognitive function in a small sample of RRMS and SPMS patients [11], and decreased visual-cognitive performance in MS measured by the King-Devick test [29]. Importantly, similar relationships within the visual-cognition axis have been implicated in other neurological disorders, including Alzheimer's disease [30] and Parkinson's disease [31]. Thus, impairment to the visual-cognitive system may be an important sequela of broad neurological damage, and in MS, thereby provides further support for their potential utility as complementary outcomes to both MRI and clinical measures for assessing neuroprotection in MS.

Impaired neuropsychological function may influence low-contrast visual function performance. LCLA measurement is more challenging, and requires greater concentration, attention and memory than HCVA assessment. As such, LCLA evaluation may require a greater degree of cortical visual processing and recruit higher cortical function input. Impaired cognitive function in MS, therefore, may influence performance in LCLA assessment. Indeed, across the cohort, the cognitive domains predominantly associated with LCLA performance included processing speed (SDMT), and visual learning (BVMT-R). Unlike HCVA, LCLA has been shown to detect treatment effects that manifest as reduced likelihood of visual loss [32] and greater likelihood of visual improvement [33]. LCLA may

be a more sensitive measure of visual dysfunction related to optic neuropathy, and since structural measures of optic neuropathy such as GCIP thickness have been shown to strongly reflect global brain atrophy, this may additionally help explain why LCLA appeared to more broadly reflect global cognitive function in the study cohort as compared to HCVA.

Conversely, impaired visual function may influence cognitive performance. Specifically, the interplay between both neuropsychological function and visual pathway damage with low-contrast visual function may impede performance on vision-dependent cognitive tests. For example, the associations between LCLA and BVMT-R TR and DR scores were particularly robust and striking across the cohort and within RRMS, suggesting lower LCLA scores reflect lower BVMT-R scores. This observation may have important implications in clinical trials that include vision-dependent cognitive tests such as BVMT-R as a functional outcome measure, which may be skewed by poor LCLA. Therefore, caution may need to be taken in interpreting results of clinical trials not accounting for visual impairment in the interpretation of BVMT-R results, or, for future clinical trials, there may be a necessity to screen participants with impaired LCLA.

Since neurodegeneration may be a more prominent pathobiological feature of PMS than RRMS, we hypothesized that VP measures would better reflect global cognitive function particularly in PMS. However, relationships between structural (GCIP thickness) and functional (VA) measures of VP degeneration and cognitive function were generally lacking in PMS. A major contributory factor underlying this finding may be the small sample size of the PMS cohort (n=36). Additionally, the observed lack of association between visual pathway measures and cognitive outcomes may reflect basement or floor effects (e.g. PMS patients may have reached a point in their disease course in which visual function, GCIP thickness and/or cognitive function scores could not be any lower than measured), thereby skewing and/or masking potential relationships [1, 21, 34, 35]. For these reasons, our finding of VP measures being predominantly associated with cognition in RRMS, as opposed to PMS, should be cautiously interpreted. This being said, the relationships observed between VP and neuropsychological measures also appeared to differ between RRMS and PMS warranting further exploration in future studies. Future studies examining the relationships between VP measures and cognition, as well as measures of depression and impact of fatigue in MS, should include much larger cohorts of PMS patients in order to more accurately elucidate and characterize such relationships. Moreover, future studies should also assess the longitudinal relationships between VP and neuropsychological measures.

Decreased GCIP thickness has been shown to be associated with high Expanded Disease Disability Status (EDSS) scores, lower whole brain volume, and particularly, gray matter volume [36]. Additionally, macular RNFL and GCIP thicknesses have been correlated with volumes of the insular and cingulate cortices, two domains responsible for cognition in RRMS [37]. Indeed, GCIP thickness was associated with DKEFS scores and average retinal thickness was associated with BVMT-R DR and DKEFS scores. However, there was a paucity of general associations between OCT measures and cognition. This being said, we hypothesized that GCIP thickness would only partially reflect cognitive function in MS, and since multiple cognitive domains are necessary to perform high, and in particular low-

contrast visual function assessment, that visual function would more greatly reflect neuropsychological function in MS than GCIP thickness.

In addition to the aforementioned limitations, the cohort included was heterogeneous in that study participants varied according to MS disease-modifying therapies, and this heterogeneity, in addition to the varying degrees of treatment switches occurring prior to the study, is difficult to account for in analyses. Accordingly, effects of disease modifying therapies on the study results cannot be excluded. Further, it is necessary to exercise caution when interpreting our findings, as the study lacked analyses with healthy controls. As such, it is not possible to definitively establish that the observed relationships are in their entirety directly related to the pathobiology of the MS disease process, in the absence of similar detailed neuropsychological assessments and analyses in healthy controls. Additionally, the present study lacked refraction testing, which has been shown to improve habitual visual acuity [38] and may be a potential limitation of our study. However, all patients in the current study received routine, high-quality ophthalmological care, including extensive visual assessments, and therefore had optimized corrective lenses. This is a standard of care for all patients with MS receiving care at our center. Given this, combined with the generally younger age of our patient cohort, it is therefore unlikely that performing same-day refractions in the current study participants would have had a significant impact on the study outcomes. Moreover, from a patient burden perspective, refractions could not be justified in all participants in this relatively large-sized cohort who were already undergoing extensive, time-consuming visual and cognitive testing. Similarly, due to the already extensive study protocols, the current study did not include near-visual acuity tests, which have been previously useful in accounting for the effects of mild visual disturbances on vision-dependent cognitive tests such as SDMT and BVM-T-R [39]. Future studies should address these limitations.

In conclusion, this study reveals a broad range of relationships between VP measures, particularly visual acuity (and OCT parameters to a lesser extent), and neuropsychological function in MS. The relationships between LCLA and cognitive function, particularly in RRMS, were striking and consistent. Overall, the study findings support the concept that VP measures reflect global aspects of the MS disease process, including broad domains of cognitive functioning, aspects of the MS disease process that are clinically relevant and extremely important. As such, our study further supports VP measures as useful biomarkers, not only for monitoring disease progression and providing valuable insight regarding global disability complementary to MRI and clinical measures, but also as potential outcome measures in clinical trials of putatively neuroprotective and/or remyelinating therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT

J. Nguyen: data collection, data analysis, interpretation of data, drafting, and revision of manuscript. A. Rothman: data collection and revision of manuscript for important intellectual content. Dr. Fitzgerald: data analysis, revision of manuscript for important intellectual content. Dr. Balcer: revision of manuscript for important intellectual

content. Dr. Frohman: revision of manuscript for important intellectual content. T. Frohman: revision of manuscript for important intellectual content. Dr. Crainiceanu: data analysis, interpretation of data, drafting and revision of manuscript for important intellectual content. Dr. Meghan Beier: data analysis, interpretation of data, drafting and revision of manuscript for important intellectual content. Dr. Newsome: drafting and revision of manuscript for important intellectual content. Dr. Calabresi: data collection, interpretation of data, drafting and revision of manuscript for important intellectual content. Dr. Saidha: data collection, data analysis, interpretation of data, drafting and revision of manuscript for important intellectual content.

FUNDING

This study was funded by Race to Erase MS (to S.S.); National Institute of Health (5R01NS082347-02 [to P.A.C.]); National Multiple Sclerosis Society (RG-1606-08768 [to SS]; TR 3760-A-3 [to P.A.C.] & RG 4212-A-4 [to L.J.B. subcontracted to P.A.C.]); National Eye Institute (R01 EY 014933 & R01 EY 019473 [to L.J.B. subcontracted to P.A.C.]); and Braxton Debbie Angela Dillon & Skip (DADS) Donor Advisor Fund (to P.A.C., E.M.F., and L.J.B.).

REFERENCES

1. Saidha S, Al-Louzi O, Ratchford JN, Bhargava P, Oh J, Newsome SD, Prince JL, Pham D, Roy S, Zijl P, et al. Optical coherence tomography reflects brain atrophy in multiple sclerosis: a four-year study. *Ann Neurol*. 2015; 78(5): 801–813. [PubMed: 26190464]
2. Saidha S, Syc SB, Durbin MK, Eckstein C, Oakley JD, Meyer SA, Conger A, Frohman TC, Newsome S, Ratchford JN, et al. Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness. *Mult Scler J*. 2011; 17(12): 1449–63.
3. Talman LS, Bisker ER, Sackel DJ, Long DA, Jr, Galetta KM, Ratchford JN, Lile DJ, Farrell SK, Loguidice MJ, Remington G, et al. Longitudinal study of vision and retinal nerve fiber layer thickness in MS. *Ann Neurol*. 2010; 67(6): 749–760. [PubMed: 20517936]
4. Walter SD, Ishikawa H, Galetta KM, Sakai RE, Henderson SB, Wilson JA, Maguire MG, Galetta SL, Frohman E, Calabresi PA, et al. Ganglion cell loss in relation to visual disability in multiple sclerosis. *Ophthalmology*. 2012; 119(6): 1250–1257. [PubMed: 22365058]
5. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol*. 2008; 7(12): 1139–1151. [PubMed: 19007738]
6. Dusankova JB, Kalincik T, Havrdova T, Benedict RH. Cross cultural validation of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Clin Neuropsychol*. 2012; 26(7): 1186–200. [PubMed: 23034066]
7. Ratchford JN, Saidha S, Sotirchos ES, Oh JA, Seigo MA, Eckstein C, Durbin MK, Oakley JD, Meyer SA, Conger A, et al. Active MS is associated with accelerated retinal ganglion cell/inner plexiform layer thinning. *Neurology*. 2013; 80(1): 47–54. [PubMed: 23267030]
8. El Ayoubi NK, Ghassan S, Said M, Allam J, Darwish H, Khoury SJ. Retinal measures correlated with cognitive and physical disability in early multiple sclerosis. *J Neurol*. 2016; 263(11): 2287–2295. [PubMed: 27544501]
9. Ashtari F, Emami P, Akbari M. Association between retinal nerve fiber layer thickness and magnetic resonance imaging findings and intelligence in patients with multiple sclerosis. *Adv Biomed Res*. 2015; 4: 223. [PubMed: 26682201]
10. Toledo J, Sepulcre J, Salinas-Alaman A, Garcia-Layana A, Murie-Fernandez M, Bejarano B, Villoslada P. Retinal nerve fiber layer atrophy is associated with physical and cognitive disability in multiple sclerosis. *Mult Scler J*. 2008; 14(7): 906–912.
11. Feaster HT, Bruce JM. Visual acuity is associated with performance on visual and non-visual neuropsychological tests in multiple sclerosis. *Clin Neuropsychol*. 2011; 25(4): 640–651. [PubMed: 21512957]
12. Wieder L, Gade G, Pech LM, Zimmermann H, Wernecke KD, Dörr JM, Bellmann-Strobl J, Paul F, Brandt AU. Low contrast visual acuity testing is associated with cognitive performance in multiple sclerosis: a cross-sectional pilot study. *BMC Neurol*. 2013; 13:167. [PubMed: 24206900]
13. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Ann Neurol*. 2011; 69(2): 292–302. [PubMed: 21387374]

14. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof B, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014; 83: 278–86. [PubMed: 24871874]
15. Saidha S, Syc SB, Ibrahim MA, Eckstein C, Warner CV, Farrell SK, Oakley JD, Durbin MK, Meyer SA, Balcer LJ, et al. Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. *Brain*. 2011; 134(pt 2): 518–533. [PubMed: 21252110]
16. Schippling S, Balk LJ, Costello F, Albrecht P, Balcer L, Calabresi PA, Frederiksen JL, Frohman E, Green AJ, Klistorner A, et al. Quality control for retinal OCT in multiple sclerosis: validation of the OSCAR-IB criteria. *Mult Scler*. 2015; 21(2): 163–70. [PubMed: 24948688]
17. Tewarie P, Balk L, Costello F, Green A, Martin R, Schippling S, Petzold A, et al. The OSCAR-IB consensus criteria for retinal OCT quality assessment. *PLoS One*. 2012; 7(4):e34823. [PubMed: 22536333]
18. Bhargava P, Lang A, Al-Louzi O, Carass A, Calabresi PA, Saidha S. Applying an open-source segmentation algorithm to different OCT devices in multiple sclerosis patients and healthy controls: Implications for clinical trials. *Mult Scler Int J*. 2015; 2015: 136295.
19. Smith A Symbol digit modalities test manual. Los Angeles (CA): Western Psychological Services; 1973.
20. Fischer JS, Jak AJ, Kniker JE, Rudick RA, Cutter G. Multiple sclerosis functional composite: administration and scoring manual. National multiple sclerosis society; 2001.
21. Benedict RHB. Brief Visuospatial Memory Test - Revised, professional manual. Lutz (FL): PAR; 1997.
22. Ross T, Calhoun E, Cox T, Wenner C, Kono W, Pleasant M. The reliability and validity of qualitative scores for the Controlled Oral Word Association Test. *Arch Clin Neuropsychol*. 2007; 22(4): 475–488. [PubMed: 17317094]
23. Benton A Benton Judgment of Line Orientation Form V. Richmond (CA): Neuropsychological Assessments Inc; 1994.
24. Delis D, Kaplan E, Kramer J. Delis-Kaplan Executive Function System (D-KEFS). San Antonio (TX): Pearson Clinical Psychology; 2001.
25. Bender R, Lange S. Adjusting for multiple testing--when and how? *J Clin Epidemiol*. 2001; 54(4): 343–9.
26. Benedict RHB, Cookfair D, Gavett R, Gunther M, Munschauer F, Garg N, Weinstock-Guttman B. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J Int Neuropsychol Soc*. 2006; 12(4):549–558. [PubMed: 16981607]
27. Drake AS, Weinstock-Guttman B, Morrow SA, Hojnacki D, Munschauer FE, Benedict RH. Psychometrics and normative data for the Multiple Sclerosis Functional Composite: replacing the PASAT with the Symbol Digit Modalities Test. *Mult Scler*. 2010; 16(2):228–337. [PubMed: 20028710]
28. Balcer LJ, Frohman E. Evaluating loss of visual function in multiple sclerosis as measured by low-contrast letter acuity. *Neurology*. 2010; 74(Suppl 3):S16–S23 [PubMed: 20421569]
29. Hainline C, Rizzo JR, Hudson TE, Dai W, Berkemeier J, Raynowska J, Nolan RC, Hasanaj L, Selesnick I, Frohman TC, et al. Capturing saccades in multiple sclerosis with a digitized test of rapid number naming. *J Neurol*. 2017; 264(5):989–998. [PubMed: 28389741]
30. Rizzo R, Anderson SW, Dawson J, Nawrot M. Vision and cognition in Alzheimer's disease. *Neuropsychologia*. 2000; 38(8):1157–1169. [PubMed: 10838150]
31. Crucian GP, Okun MS. Visual-spatial ability in Parkinson's disease. *Front Biosci*. 2003; 8:s992–7. [PubMed: 12957858]
32. Balcer LJ, Galetta SL, Calabresi PA, Confavreux C, Giovanonni G, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Miller DH, et al. Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. *Neurology*. 2007; 68(16):1299–304. [PubMed: 17438220]
33. Balcer LJ, Galetta SL, Polman CH, Eggenberger E, Calabresi PA, Zhang A, Scanlon JV, Hyde R. Low-contrast acuity measures visual improvement in phase 3 trial of natalizumab in relapsing MS. *J Neurol Sci*. 2012; 318(1-2): 119–24. [PubMed: 22521274]

34. Bever CT, Jr., Grattan HS, Panitch HS, Johnson KP. The brief repeatable battery of neuropsychological tests for multiple sclerosis: a preliminary serial study. *Mult Scler.* 1995(1): 165–169. [PubMed: 9345448]
35. Freeman JA, Hobart JC, Langdon DW, Thompson AJ. Clinical appropriateness: a key factor in outcome measure selection: the 36 item short form health survey in multiple sclerosis. *J Neurol Neurosurg Psych.* 2000; 68:150–156.
36. Saidha S, Sotrichos ES, Oh J, Syc SB, Seigo MA, Shiee N, Eckstein C, Durbin MK, Oakley JD, Meyer SA, et al. Retinal axonal and neuronal measures in multiple sclerosis reflect global CNS pathology. *JAMA Neurol.* 2013 70(1):34–43. [PubMed: 23318513]
37. Stelmann JP, Cetin H, Young KL, Hodeck S, Pöttgen J, Bittersohl D, Hassenstein A, Oberwahrenbrock T, Heesen C, Siemonsen S. Pattern of gray matter volumes related to retinal thickness and its association with cognitive function in relapsing-remitting MS. *Brain Behav.* 2016; 7(2): e00614. [PubMed: 28239524]
38. Pointer JS. Habitual vs optimal distance visual acuity. *Ophthalmic Physiol Opt.* 2008; 28:457–466. [PubMed: 18761483]
39. Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, Chelune GJ, Fisk JD, Langdon DW, Caruso L, et al. Minimal neuropsychological assessment of MS patients: a consensus approach. *Clin Neuropsychol.* 2002; 16:381–397. [PubMed: 12607150]

Figure 1.

Adjusted-variable plots illustrating significant relationships between high- and low-contrast visual function with BVMT-R total recall scores in RRMS, adjusting for sex, disease duration, years of education, and optic neuritis history.

Table 1.

Neuropsychological tests and fatigue and depression surveys administered

Measure	Domain
Multiple Sclerosis Functional Composite (MSFC) ^{1*}	Working memory, complex concentration, information processing speed lower extremity and fine motor skills
Symbol Digit Modalities Test (SDMT) ^{2*}	Information processing speed, visual scanning, working memory
Brief Visuospatial Memory Test (BVM-T-R) Total Recall ^{3*}	Visual learning
BVM-T-R Delayed Recall ^{3*}	Visual delayed free recall
Judgment of Lines Orientation (JLO)	Visuospatial functioning
Controlled Oral Word Association Test (COWAT) ²	Phonemic fluency, executive functioning
Delis-Kaplan Executive Function System (DKEFS) Sorting [*]	Problem solving, cognitive flexibility, executive functioning
American National Adult Reading Test (AMNART)	Pre-morbid intelligence
Beck Depression Inventory II (BDI)	Self-reported depressive symptoms
Modified Fatigue Impact Scale (MFIS)	Self-reported impact of fatigue on physical, cognitive, and psychosocial function

¹ z-scores for each sub-test were averaged into a composite z-score. Participants who could not complete the 25-foot walk or 9-hole peg test due to disability received a 0 and were only assessed based on the other scores

² z-scores were adjusted for age and years of education

³ z-scores were adjusted for age Higher z-scores on cognitive function tests indicate better performance. Higher BDI and MFIS scores indicate greater self-reported depressive symptoms and impact of fatigue, respectively.

^{*} z-scores were used in regression analyses. Otherwise, raw scores were utilized in analyses.

Table 2.

Summary of demographics and clinical characteristics

	Overall n=131 (eyes=162)	RRMS n=95 (eyes=190)	Progressive MS n=36 (eyes=72)	p-value RRMS vs. PMS
Mean age, years (SD)	45 (12.3)	41 (11.5)	55 (8.1)	< 0.001 ¹
Mean disease duration, years (SD)	11 (8.8)	8.6 (6.6)	18.3 (9.9)	< 0.001 ¹
Females (%)	66	65	67	0.8317 ²
Race				
Caucasian	112	79	33	0.1260 ³
African American	11	9	2	
Other	8	7	1	
Patients with ON History (%)	47 (36)	39 (41)	8 (22)	0.0191 ²
Eyes with ON History (%)	56 (35)	47 (25)	9 (13)	0.0299 ²
Mean years of education (SD)	16.3 (2.1)	16.4 (2.1)	16.1 (1.9)	0.3506 ¹
Median EDSS score	3	2.5	6	< 0.001 ¹

¹Computed with Wilcoxon rank-sum test

²Computed with chi-square test

³Computed with Fisher exact test

Table 3. Relationships between VP measures and neuropsychological function across the entire MS cohort

Scores	Visual Pathway Measures									
	Average GCIP Thickness		Average Retinal Thickness		100%-VA		2.5%-LA		1.25%-LA	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
MSFC (n=93) ^a	-0.18	0.78	-0.25	0.86	0.62	0.34	0.21	0.80	-0.17	0.81
SDMT (n=69) ^b	0.43	0.56	0.62	0.70	1.28	0.90	1.61	0.09	2.17	0.005
BVMT-R Total recall (n=63) ^c	0.13	0.08	0.27	0.11	0.21	0.002	0.27	0.006	0.31	<0.001
BVMT-R Delayed recall (n=63) ^c	0.07	0.26	0.19	0.20	0.19	0.006	0.06	0.45	0.15	0.039
JLO (n=30) ^a	-0.09	0.79	0.25	0.73	0.29	0.18	-0.09	0.82	0.41	0.21
DKEFS (n=24) ^a	0.73	0.22	1.53	0.23	-0.34	0.51	0.52	0.48	0.32	0.63
COWAT (n=31) ^b	0.06	0.59	0.13	0.59	0.08	0.38	0.16	0.31	0.11	0.41
BDI (n=26) ^d	0.22	0.18	0.36	0.32	-0.10	0.39	-0.07	0.66	-0.05	0.76
MFIS (n=69) ^d	0.06	0.19	0.10	0.29	<i>0.11</i>	<i>0.07</i>	0.09	0.15	0.04	0.43

p-values and beta-coefficients (β) were derived from the mixed effect linear regression model and were adjusted for:

^a age, sex, disease duration, years of education, and ON history

^b sex, disease duration, and ON history

^c sex, disease duration, years of education, and ON history

^d age, sex, disease duration, and ON history

GCIP = Ganglion Cell and Inner Plexiform; VA = visual acuity; LA = letter acuity; MSFC = multiple sclerosis functional composite; SDMT = symbol digit modalities test; BVMT-R = Brief Visuospatial Memory Test-revised; JLO = Benton Judgement of Line Orientation; DKEFS = Delis-Kaplan Executive Function System Sorting; COWAT = Controlled Oral Word Association Test; BDI = Beck Depression Inventory II; MFIS = Modified Fatigue Impact Scale No relationships between AMNART and VP measures were found. Bolded results indicate significant *p*-values. Italicized results indicate relationships trending towards significance.

Relationships between visual pathway measures and neuropsychological function in RRMS

p-values and beta-coefficients (β) were derived from the mixed effect linear regression model, and *t*-values from partial correlation analyses, with both models adjusting for:

 $d_{\text{age, sex, disease duration, and ON history}}$

GCIP = Ganglion Cell and Inner Plexiform; VA = visual acuity; MSFC = multiple sclerosis functional composite; SDMT = symbol digit modalities test; BVMTR = Brief Visuospatial Memory Test-revised; JLO = Benton Judgement of Line Orientation; DKEFS = Delis-Kaplan Executive Function System Sorting; COWAT = Controlled Oral Word Association Test; BDI = Beck Depression Inventory II; MFIS = Modified Fatigue Impact Scale No relationships between AMNART scores and VP measures were found. Bolded results indicate significant *p*-values. Italicized results indicate relationships trending towards significance.