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RESEARCH ARTICLE

The Relationship Between Retinal Layer Thickness and Cognition in People with Multiple Sclerosis

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Abstract

Objective: Optical coherence tomography (OCT) and OCT-angiography (OCT-A) are non-invasive techniques for investigating retinal layers and blood flow. Axonal loss in neurodegenerative disorders like multiple sclerosis (MS) can be evaluated with OCT. The retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer (GCIPL) are mainly affected layers by MS-related axonal loss. As a result, these layers can be a biomarker of disability, cortical volume and cognition in people with MS (pwMS). This study investigates the relationship between cognition and retinal nerve layers' thickness and retinal vessel density in pwMS.

Materials and Methods: The participants' OCT and OCT-A examinations were evaluated retrospectively. The participants with a history of bilateral optic neuritis and less than 12 years of education were excluded from the study. The participants were divided into the following two groups: pwMS with optic neuritis (ON+) and pwMS without optic neuritis (ON-). The unaffected eyes were evaluated in the ON+, and the mean values of eyes were evaluated in the ON- group. Demographic variables, Expanded Disability Status Scale (EDSS) and Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), which include: Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test-Revised (BVMT-R), California Verbal Learning Test-II (CVLT-II) were examined.

Results: Twenty-eight participants were in the ON+ group, and 56 pwMS were in the ON- group. The thickness of GCIPL inferior and temporal quadrants exhibited a weak negative correlation with BVMT-R in the ON-group. The vessel density of optic disc inferior quadrant results showed a weak positive correlation with SDMT in the ON-group (ρ=0.329, p=0.02). The superonasal quadrant of RNFL had a moderate negative correlation with the results of CVLT-II in the ON+ group (ρ=-0.458, p=0.016). On the other hand, GCIPL, in all quadrants except the centrum, positively correlated with SDMT in the ON+ group. Similar correlation results were detected between the inferotemporal/global thickness of RNLF and SDMT in the ON+ group.

Conclusion: The thicknesses of specific quadrants of RNFL and GCIPL might have a weak to moderate correlation with information processing speed, particularly in ON+ pwMS. Only inferior quadrant optic disc vessel density showed a weak correlation with information processing speed in ON- group.

Keywords: Optical coherence tomography, optical coherence tomography-angiography, cognition, multiple sclerosis

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Introduction

Multiple sclerosis (MS) is primarily a demyelinating immune-mediated disorder that affects the central nervous system. Neurodegeneration and axon loss are also key pathophysiological contributors of progression and disability (1). Optical coherence tomography (OCT), which provides direct visualization of retinal layers, is an efficient method to detect axonal loss in people with MS (pwMS). Axonal degeneration in certain retinal layers can show disability accumulation and brain atrophy in pwMS with and without optic neuritis (2).

Another possible pathogenic cause of MS is central nervous system microvascular damage and hypoxia (3,4). Low cerebral blood perfusion in pwMS and low grey matter perfusion in pwMS were associated with worse cognitive skills (5). Retinal structures were derived embryonically from similar places to the central nervous system. Vascular structures and the retinal blood barrier also showed similarities with the central nervous system (6). So, the similar pathogenic mechanisms that are seen in central nervous system microvascularity can be seen in retinal vascularity. Retinal microvascular damage can be detected in pwMS and detected via OCT-angiography (OCT-A) (7-9). Although the results vary, disability accumulation may be associated with different OCT-A measurements (9-13). Further, the measurements of OCT-A might be related to grey and white matter atrophy in pwMS, and a longitudinal decrease might be associated with worsening Expanded Disability Status Scale (EDSS), brain atrophy or cognitive skills (14).

Cognitive impairment can be detected in 30-75% of pwMS. These deficits are more common in progressive MS groups (15). Axonal loss and neurodegeneration are the main factors in irreversible cognitive impairment in pwMS, and OCT can detect these conditions by measuring the retinal layers (16). Although the results were contradictory, the retinal nerve fiber layer (RNFL) correlates with the Symbol Digits Modality Test (SDMT), California Verbal Learning Test (CVLT) and Brief Visuospatial Memory Test-Revised (BVMT-R) (17,18). Also, atrophy in the RNFL can predict further cognitive impairment (19,20). Studies presented different results regarding the relationship between Ganglion cell inner plexiform layer (GCIPL) thickness and cognition (17,18). On the other hand, while research indicated that cerebral hypoperfusion may have a correlation with cognitive skills in pwMS, limited studies investigated the relationship between cognition and OCT-A results (14).

In this study, we hypothesized that retinal thickness and retinal microvascular density could be a reliable biomarker for cognitive status in relapsing-remitting MS. For this purpose, we investigated the OCT and OCT-A measurements and their relation to cognitive tests of pwMS.

Materials and Methods

This cross-sectional study was approved by the Non-invasive Research Ethics Board of Dokuz Eylul University (protocol no.: 6546-GOA, decision no.: 2021/22-03). The study included individuals with relapsing-remitting pwMS with at least one OCT/OCT-A test during their follow-up. The OCT and OCT-A results were examined retrospectively. The thicknesses of retinal layers -macular Ganglion Cell Inner Plexiform Layer (GCIPL) and peripapillary Retinal Nerve Fiber Layer (RNFL)- in different areas were studied. Global thickness, four quadrants and two regions were examined separately for RNFL (SN=Superionasal/ST=Superiotemporal/IN=Inferonasal/IT=Inferotemporal/T=Temporal/N=Nasal). The central region and quadrants were analysed independently in the context of GCIPL analysis (C=Central/S=Superior/I=Inferior/T=Temporal/N=Nasal). The vessel density of the macula and the optic disk were considered in parts of the central region and quadrants (M=Macula and D=Optic disc/S=Superior/I=Inferior/T=Temporal/N=Nasal). If a participant had no history of optic neuritis, the mean values of both eyes were analysed. If a participant had a history of optic neuritis, the non-affected eye was examined. Statistical analyses were done separately in pwMS without optic neuritis (ON-) and with optic neuritis (ON+). To interpret the correlation of cognitive status and OCT/OCTA measurements, Brief International Cognitive Assessment in Multiple Sclerosis (BICAMS, which includes SDMT, BVMT-R and CVLT-II) results in the period of OCT tests were analysed. In our study design, there was no healthy control. Because of the fact that education level might have caused differences in cognitive tests, we only included the pwMS with ≥12 years of education level. The participants who had MS relapse during cognitive assessments and OCT/OCTA or a history of bilateral optic neuritis were excluded from the study. Data on gender, age, diagnosis age, and EDSS were collected and analysed.

Statistical Analysis

Data were analysed using the IBM SPSS (Version 26.0. Armonk, NY: IBM Corp.) program. Normal distribution was determined by Kolmogorov-Smirnov/Shapiro-Wilk tests. According to the distribution results, appropriate statistical analysis methods were used. Chi-square tests were used to compare categorical variables between groups. If the distribution was normal, we used the Pearson correlation test for analysis. If the distribution was non-normal, a Spearman test was used. The correlation results were labelled the strength of the association for absolute values of correlation coefficients, 0.2-0.39 as weak, 0.4-0.59 as moderate, 0.6-0.79 as strong, and 0.8-1 as very strong. The statistical significance level was determined as $p<0.05$.

Results

A total of 84 pwMS were included in the study. Twenty-eight participants had a history of ON+ group, and 56 pwMS had no history of optic neuritis (ON- group). There were no differences between the groups regarding EDSS, BVMT-R, CVLT-II, SDMT, number of relapses, gender, diagnosing age and current age (p>0.05) (Table 1).

In the ON- group, 50 pwMS had OCT test results, and 56 had OCT-A results. So, 100 eyes in OCT and 112 in OCT-A were interpreted. The relapse number had a weak negative correlation with the inferior quadrant of OCTA-D (OCTA-D-I: ρ=-0.325, p=0.021). The thickness of GCIPL inferior and temporal quadrants exhibited a weak positive correlation with BVMT-R (Table 2). Only OCTA-D-I results had a weak negative correlation with SDMT in OCTA measurements (ρ=0.329, p=0.02, Table 2).

In the ON+ group, 27 pwMS had OCT results, and 28 had OCT-A results. The number of relapses had a negative correlation with RNFL-ST (ρ=-0.481, p=0.011). Only the SN quadrant of RNFL had a moderate negative correlation with the results of CVLT-II (ρ=-0.458, p=0.016). On the other hand, GCIPL, in all quadrants except the centrum, positively correlated with SDMT. Similar correlation results were detected between the inferotemporal/global thickness of RNLF and SDMT. Cognitive tests, relapse number, EDSS score or age did not show a correlation with OCT-A measurements (Table 3).

Discussion

The findings of this study indicated that certain parts of the retinal layer may suggest cognitive impairment in people with MS. However, vascular density in the retina may not be a reliable biomarker for the cognitive condition of people with relapsing-remitting MS.

The first study, published in 2008, revealed that retinal layer thickness can indicate cognitive status in pwMS. Temporal RNFL thickness was especially related to SDMT in this study (21). Studies demonstrated that average RNFL and GCIPL thickness might correlate with cognitive abilities in pwMS (19,22-25). The regions of RNFL and GCIPL might contribute to this relationship in different portions. For instance, the temporal region of RNFL especially demonstrates a positive correlation with SDMT in the studies (21,26). However, certain parts of the studies did not demonstrate the relation between cognition and the thickness of the retinal layers (27,28). Petracca et al. (29) conducted a study in people with primary progressive MS, indicating that only GCIPL atrophy represents cognitive impairment. The history of optic neuritis causes severe atrophy and may mask the cognitive relations of it (22). Some studies analysed the OCT results of pwMS with and without optic neuritis (21). To avoid this situation, we divided our cohort into ON+ and ON- groups and included the only non-affected eye for analyses in the ON+ group. ON- group, inferior and temporal quadrants of GCIPL negatively correlated in specific cognitive tests. Atrophy of RNLF did not show a correlation with cognitive impairments (Table 2). These findings contradict the current literature. However, the negative correlation was quite weak. It could be due to the cognitive reserve of pwMS. People with MS who had similar disability levels and similar brain lesion load may have differences in cognitive tests. Cognitive reserve, which occurs through education, intelligence, etc. can explain this situation. Cognitive reserve can play a protective role in cognitive skills and moderate the results of cognitive tests in pwMS (30,31). Some participants might have a high cognitive reserve, which can cause these results in our study. On the other hand, studies found no correlation between retinal layer thickness and cognition in pwMS with low EDSS scores (27,28). Our participants also have low EDSS scores, and we found no association between cognitive skills and OCT measurements in the ON- group (The median EDSS score in ON- =0.5). Axonal loss and neurodegeneration in pwMS can be seen throughout the disease. However, they are more evident in progressive and high-disability patients (32). So, brain atrophy, cognitive impairments and axonal loss in pwMS are more evident in these groups.

Table 1. Demographic variables of pwMS with optic neuritis (ON+) and without optic neuritis (ON-)

	ON+	ON-	Statistics (p)
Total participants, n	28	56	
Gender, n of females, percentage	14/28 (50%)	40/56 (71.4%)	0.053
Age, median, Min.-Max.	29.5, 19-47	34, 18-56	0.414
Diagnosing age, median, Min.-Max.	26, 16-40	27, 16-44	0.872
Relapse number, median, Min.-Max.	2, 1-8	2, 1-10	0.957
EDSS score, median, Min.-Max.	0.5, 0-5.5	1, 0-2.5	0.205
BVMT-R, median, Min.-Max.	29.5, 11-36	29.5, 11-36	0.996
CVLT-II±SD	52.89±13.97	54.84±10.62	0.385
SDMT±SD	53.79±12.56	52.45±11.26	0.891

n: Number, EDSS: Expanded Disability Status Scale, BVMT-R: Brief Visuospatial Memory Test-Revised, CVLT-II: California Verbal Learning Test-II, SDMT: Symbol Digit Modalities Test, SD: Standard deviation, Min.-Max.: Minimum-maximum

Table 2. Correlation analysis of ON- pwMS

	BVMT-R	SDMT	CVLT-II	EDSS	N of relapses	Current age	MS diagnosing age
RNFL-G	ρ=-0.183	r=0.149	r=0.029	ρ=0.010	ρ=-0.124	ρ=-0.088	ρ=0.050
RNFL-ST	ρ=-0.185	r=0.260	r=0.074	ρ=-0.050	ρ=-0.145	ρ=0.045	ρ=0.212
RNFL-SN	ρ=-0.227	r=0.157	r=-0.188	ρ=0.008	ρ=-0.135	ρ=-0.148	ρ=-0.087
RNFL-IT	ρ=-0.168	r=0.040	r=-0.027	ρ=-0.031	ρ=0.030	ρ=0.026	ρ=0.125
RNFL-IN	ρ=-0.275	r=-0.181	r=0.021	ρ=0.180	ρ=0.023	ρ=-0.022	ρ=0.025
RNFL-N	ρ=-0.067	r=0.167	r=0.234	ρ=-0.022	ρ=-0.086	ρ=-0.050	ρ=0.075
RNFL-T	ρ=-0.096	r=0.117	r=-0.047	ρ=0.102	ρ=-0.216	ρ=0.030	ρ=0.235
GCIPL-C	ρ=0.13	ρ=0.275	ρ=-0.117	ρ=0.000	ρ=-0.08	ρ=-0.104	ρ=0.02
GCIPL-S	ρ=-0.256	ρ=0.156	ρ=-0.106	ρ=0.089	ρ=-0.218	ρ=-0.076	ρ=0.114
GCIPL-I	ρ=-0.34 p=0.014	ρ=0.117	ρ=-0.059	ρ=0.163	ρ=-0.167	ρ=-0.032	ρ=0.31
GCIPL-N	ρ=-0.24	ρ=0.278	ρ=-0.198	ρ=0.107	ρ=-0.251	ρ=-0.211	ρ=-0.028
GCIPL-T	ρ=-0.303 p=0.032	ρ=0.179	ρ=-0.138	ρ=-0.000	ρ=-0.080	ρ=-0.104	ρ=0.020
OCTA-M-C	ρ=-0.01	r=-0.168	r=-0.254	ρ=-0.055	ρ=0 .011	ρ=-0.003	ρ=-0.052
OCTA-M-S	ρ=-00.141	r=-0.088	r=-0.045	ρ=0.242	ρ=-0.004	ρ=0.136	ρ=0.057
OCTA-M-I	ρ=0.089	ρ=0.022	ρ=0.08	ρ=0.005	ρ=-0.06	ρ=0.131	ρ=0.096
OCTA-M-N	ρ=0.222	ρ=-0.11	ρ=0.035	ρ=-0.02	ρ=-0.048	ρ=0.086	ρ=0.121
OCTA-M-T	ρ=-0.005	r=-0.014	r=0.064	ρ=-0.111	ρ=-0.154	ρ=-0.074	ρ=-0.154
OCTA-D-C	ρ=-0.048	r=0.044	r=0.109	ρ=-0.114	ρ=-0.114	ρ=-0.032	ρ=-0.037
OCTA-D-S	ρ=0.092	r=0 .017	r=-0.257	ρ=-0.203	ρ=-0.203	ρ=-0.355	ρ=-0.273
OCTA-D-I	ρ=0.178	ρ=0.195	**ρ=0.329 p=0.02**	ρ=-0.109	**ρ=-0.325 p=0.021**	ρ=-0.172	ρ=0.007
OCTA-D-N	ρ=-0.137	r=-0.123	r=0.144	ρ=-0.036	ρ=-0.036	ρ=0.073	ρ=0.162
OCTA-D-T	ρ=-0.162	r=-0.123	r=-0.239	ρ=0.2	ρ=-0.191	ρ=-0.11	ρ=0.081
BVMT-R	-	**ρ=0.296 p=0.027**	**ρ=0.408 p=0.002**	ρ=-0.201	ρ=-0.018	ρ=-0.157	ρ=-0.18
SDMT	**ρ=0.296 p=0.027**	-	**r=0.4 p=0.002**	ρ=-0.205	ρ=0.144	**ρ=-0.450 p=0.001**	**ρ=-0.341 p=0.01**
CVLT-II	**ρ=0.408 p=0.002**	**r=0.4 p=0.002**	-	ρ=-0.183	ρ=0.02	ρ=0.000	ρ=0.079
EDSS	ρ=-0.201	ρ=-0.205	ρ=-0.183	-	ρ=0 .075	**ρ=0.271 p=0.043**	ρ=0.078
N of relapses	ρ=-0.018	ρ=0.144	ρ=0.02	ρ=0.075	-	ρ=0.226	ρ=-0.183
Current age	ρ=-0.157	**ρ=-0.450 p=0.001**	ρ=0.000	**ρ=0.271 p=0.043**	ρ=0.226	-	**ρ=0.78 p=0.000**
MS diagnosing age	ρ=-0.18	**ρ=-0.341 p=0 0.01**	ρ=0.079	ρ=0.078	ρ=-0.183	**ρ=0.78 p=0.000**	-

A total of 50 OCT results and 56 OCTA results were considered. RNFL: Retinal Nerve Fiber Layer, G: Global, SN: Superiornasal, ST: Superiortemporal, IT: Inferotemporal, IN: Inferonasal, N: Nasal, T: Temporal, GCIPL: Ganglion Cell Internal Plexiform Layer, C: Central, S: Superior, I: Inferior, OCTA: Optical Coherence Tomography-Angiography, M: Macular, D: Disc, BVMT-R: Brief Visuospatial Memory Test-Revised, SDMT: Symbol Digit Modalities Test, CVLT-II: California Verbal Learning Test-II, EDSS: Expanded Disability Status Scale, N: Number, MS: Multiple sclerosis

Table 3. Correlation analysis of ON+ pwMS

	BVMT-R (ρ)	SDMT (ρ)	CVLT-II (ρ)	EDSS (ρ)	N of relapses (ρ)	Current age (ρ)	MS diagnosing age (ρ)
RNFL-G	-0.192	**ρ=0.424 p=0.028**	-0.043	-0.037	-0.272	-0.153	0.031
RNFL-ST	0.234	0.354	0.049	-0.183	**ρ=-0.481 p=0.011**	-0.118	0.080
RNFL-SN	-0.308	0.025	**ρ=-0.458 p=0.016**	-0.074	-0.283	0.092	0.108
RNFL-IT	0.094	**ρ=0.466 p=0.014**	0.270	-0.064	-0.332	-0.276	-0.086
RNFL-IN	-0.356	0.121	-0.243	-0.077	-0.161	0.101	0.114
RNFL-N	-0.155	0.261	-0.108	0.290	0.046	0.102	0.264
RNFL-T	0.191	0.260	0.134	-0.220	-0.124	-0.291	-0.167
GCIP-C	0.001	0.082	0.049	-0.038	0.217	0.315	0.363
GCIP-S	0.342	**ρ=0.542 p=0.003**	0.364	-0.149	-0.181	-0.358	-0.183
GCIP-I	0.108	**ρ=0.401 p=0.038**	0.154	-0.132	-0.167	-0.251	-0.107
GCIP-N	0.167	**ρ=0.441 p=0.021**	0.239	-0.081	-0.080	-0.213	-0.074
GCIP-T	0.225	**ρ=0.412, p=0.033**	0.365	-0.055	0.023	-0.278	-0.133
OCTA-M-C	0.022	0.056	0.001	0.046	-0.053	0.185	0.245
OCTA-M-S	0.150	0.280	0.088	-0.039	0.215	-0.310	-0.291
OCTA-M-I	0.172	0.003	-0.067	0.103	0.257	0.131	-0.029
OCTA-M-N	0.252	0.066	0.175	-0.217	0.188	-0.017	0.038
OCTA-M-T	0.103	0.120	-0.074	-0.034	-0.021	-0.002	0.071
OCTA-D-C	-0.061	0.182	-0.085	0.069	-0.104	-0.355	-0.336
OCTA-D-S	-0.278	-0.349	-0.246	0.080	-0.122	0.077	0.164
OCTA-D-I	-0.104	0.002	-0.014	0.075	-0.038	0.062	0.201
OCTA-D-N	-0.100	0.191	-0.189	-0.102	-0.207	0.036	0.187
OCTA-D-T	0.086	0.222	0.297	0.026	-0.062	-0.050	-0.098
BVMT-R	-	**ρ=0.432 p=0.022**	**ρ=0.724 p=0.000**	**ρ=-0.447 p=0.017**	0.001	-0.173	-0.144
SDMT	**ρ=0.432 p=0.022**	-	**ρ=0.401 p=0.034**	-0.28	**ρ=-0.398 p=0.036**	-0.190	-0.016
CVLT-II	**ρ=0.724 p=0.000**	**ρ=0.401 p=0.034**	-	-0.195	0.001	-0.161	-0.141
EDSS	**ρ=-0.447 p=0.017**	-0.28	-0.195	-	0.122	0.366	0.307
N of relapses	0.001	**ρ=-0.398 p=0.036**	0.001	0.122	-	0.281	0.118
Current age	-0.173	-0.190	-0.161	0.366	0.281	-	**ρ=0.861 p=0.000**
MS diagnosing age	-0.144	-0.016	-0.141	0.307	0.118	**ρ=0.861 p=0.000**	-

A total of 27 OCT and 28 OCTA results were considered. RNFL: Retinal Nerve Fiber Layer, G: Global, SN: Superiornasal, ST: Superiortemporal, IT: Inferotemporal, IN: Inferonasal, N: Nasal, T: Temporal, GCIPL: Ganglion Cell Internal Plexiform Layer, C: Central, S: Superior, I: Inferior, OCTA: Optical Coherence Tomography-Angiography, M: Macular, D: Disc, BVMT-R: Brief Visuospatial Memory Test-Revised. SDMT: Symbol Digit Modalities Test, CVLT-II: California Verbal Learning Test-II, EDSS: Expanded Disability Status Scale, N: Number, MS: Multiple sclerosis

The low correlation between retinal layer thickness and cognition in pwMS with low disability levels might be the main cause of these results. The disability levels of ON+ participants are similar to ON- participants (Median EDSS score in ON- =0.5 vs ON+ =1). However, in ON+, GCIPL had a moderate positive correlation with SDMT. A similar correlation was detected with the RNFL-IT quadrant and global RNLF. The SDMT evaluates information processing speed, which is the key cognitive function impaired in pwMS. It is also impaired during the early stages of MS. Thus, this relationship may be considered in this context (Table 3). The atrophy of the retinal layers might be a consequence of asymptomatic optic nerve lesions. Asymptomatic optic nerve lesions might be the primary link between brain volume loss, cognitive testing, and retinal atrophy (33). The analysis of asymptomatic optic nerve lesions may provide more information about the fact that there is no relationship between cognition and retinal atrophy in the low EDSS group. The different correlation results in the ON- and ON+ groups might be related to different percentages of asymptomatic optic nerve lesions in both groups. The participants in ON+ might have experienced more asymptomatic optic nerve lesions than the ON- group.

Microvascular damage and related hypoxia can contribute to neurodegeneration and disability in pwMS. Hypoxia in cortical and white matter regions was high in pwMS, especially with a high EDSS score and secondary progressive subtype (4,34,35). In secondary progressive MS, cortical hypoperfusion might related to low cognitive status (36). However, in another study, cortical hypoxia was not correlated with cognitive measurements in relapsing-remitting pwMS (37). Abnormal retinal microcirculation in pwMS with and without optic neuritis was demonstrated in different studies (7,11-13). However, the relationship between retinal microvascular density and disability levels in pwMS is not clear. Different studies indicated different results. A study from Turkey demonstrated no relationship between disability levels and retinal microvascular density (12). Lower superficial vessel density might be related to higher disability levels (11). However, Mrabet et al. (13) did not find this correlation in their study. They indicated that choriocapillaris density shows an inverse correlation with EDSS scores. A positive correlation between disability status and superficial retinal density was detected in another study (10). Further, retinal microvascular density can improve with time in pwMS with stable disease (38). Different demographic and clinical variables might cause these differences. Our study found no relation between OCT-A measurements and EDSS and age in both groups. Only the number of relapses exhibited a weak positive correlation with OCTA-D-I in the ON- group. Retinal superficial and deep vascular rarefication were found to be associated with grey matter atrophy independent of ganglion cell layer thickness in pwMS with low disability levels. Even a decrease in these densities was related to decreased grey matter volume and increased disability levels. Longitudinal loss in deep and superficial retinal vessels was detected more frequently in pwMS, which had worsening SDMT scores (14). This study investigated the SDMT and OCT-A measurements only in longitudinal courses. Our study considered the association between vessel density and cognition cross-sectional. Also, we considered the total BICAMS results of our participants. We found a positive correlation between CVLT-II and inferior optic disc vessel density in the ON- group. The other parts of OCT-A do not correlate with other cognitive tests (Tables 2 and 3).

Study Limitations

Our study has several limitations. The retrospective nature of the study focusing on OCT and OCT-A examinations inherently limited the participant pool, as these tests were performed based on clinical indications rather than as part of a standardized protocol. The OCT and OCT-A are ordered by ophthalmologists and neurologists in the appropriate situations. Because we had no healthy controls, we only included the pwMS who have ≥12 years of education. Larger studies and studies that include healthy controls can provide more information about the relationship between OCT, OCT-A, and cognition in wider pwMS populations. As previously stated, cognitive reserve, pwMS with a low disability, and relapsing form may create distinctions in our study. Different results between groups related to cognitive and retinal measurements might stem from a low number of participants, especially in the ON+ group, or different clinical characteristics between the groups, such as different brain atrophy stages, lesion numbers etc. Further studies considering these variables might explain these differences. Even though there are a lot of studies regarding retinal later thickness and cognitive skills, we found limited studies about retinal microcirculation and cognition. Although our results indicated a limited correlation between retinal vessel density in the inferior optic disc quadrant and cognition, further studies can be designed in wider populations and pwMS with higher disability levels.

Conclusion

The study found that OCT is limited in reflecting cognitive impairments in ON- pwMS with low disability levels. However, certain regions of GCIPL and RNFL may demonstrate a positive correlation with SDMT in ON+ pwMS. The retinal microcirculation and cognitive correlation were weak, but further studies can provide more information.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the Non-invasive Research Ethics Board of Dokuz Eylul University (protocol no.: 6546-GOA, decision no.: 2021/22-03).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.K., D.O., F.G., A.Y., C.B., Concept: S.O., A.Y., C.B., Design: S.O., O.S., Data Collection or Processing: S.O., D.O., F.G., O.S., A.Y., Analysis or Interpretation: S.O., E.K., O.S., Literature Search: S.O, E.K., Writing: S.O, E.K., A.Y., C.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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