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Letter to the Editor

Relationship between Retinal Nerve Fiber Layer Thickness and Cognitive Measures in Mild Cognitive Impairment Patients

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The authors have no financial conflicts of interest.

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Exploratory biomarkers of Alzheimer's disease (AD) are often expensive and invasive, which limits their clinical application.[1] One potential biomarker is visual-system assessment in the early stages of AD. The retina is an extension of the central nervous system and can be accessed easily via imaging techniques, such as optical-coherence tomography (OCT).[2,3] Many *in vivo* studies have investigated the accumulation of Aβ plaques and structural abnormalities in the retina of patients with AD.[2,3] Patients with mild cognitive impairment (MCI) have thinner retinal-nerve-fiber layers (RNFLs) than control subjects. A number of studies also investigated the association between RNFL thickness and cognitive function, but the results were inconsistent.[2,3] In this study, we retrospectively examined the cognitive function of patients with MCI using domain-specific neuropsychological tests, and investigated the association between RNFL thickness and cognitive function in several subdomains.

Between July 2016 and February 2020, we recruited patients with memory deterioration who visited Veterans Health Service Medical Center. We examined the medical records of 57 MCI patients according to the diagnostic criteria of the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association.[4] All participants underwent a domain-specific neuropsychological test using the Seoul Neuropsychological-Screening Battery.[5] Language function was assessed using the Korean version of the Boston Naming Test. Verbal memory was assessed using the Seoul Verbal-Learning Test. Executive function was assessed using the categorical (animal) and phonemic word-fluency scores of the Controlled-Oral-Word-Association Test. Scores that were <1 standard deviation away from the age, gender, education standard were classified as abnormal. RNFL thickness was measured in the total, superior, inferior, nasal, and temporal quadrants using DRI OCT (Topcon Corp., Tokyo, Japan) according to standard procedure (**Supplementary Fig. 1**). We performed Pearson's correlation analysis followed by linear-regression analysis to determine the independent parameters correlated with cognitive functioning of subdomains in relation to RNFL thickness, age, education year, and gender. We performed all the statistical analyses using SPSS 18 (SPSS Inc., Chicago, IL, USA). This study was approved by the Medical-Research-Ethics Committee of Veterans Health Service Medical Center (2020-07-003).

We included 57 participants in our analysis, with median age and years of education of 71 and 12 years, respectively. Ophthalmological data are shown in the **Supplementary Table 1**. Pearson's correlation analysis did not reveal any correlation between mean or quadrant RNFL

Table 1. Correlation matrix between cognitive measures and RNFL thickness

Variables	RNFL total	RNFL superior	RNFL nasal	RNFL inferior	RNFL temporal
MMSE	−0.083 (0.540)	−0.177 (0.197)	0.073 (0.595)	−0.037 (0.789)	−0.081 (0.556)
SVLT immediate recall	0.077 (0.572)	0.066 (0.626)	0.185 (0.169)	0.025 (0.855)	−0.006 (0.966)
SVLT delayed recall	−0.056 (0.679)	−0.007 (0.958)	0.028 (0.835)	−0.106 (0.434)	−0.088 (0.514)
BNT	−0.128 (0.347)	−0.159 (0.243)	−0.098 (0.471)	−0.127 (0.352)	−0.005 (0.968)
Verbal fluency categorical	0.159 (0.238)	0.183 (0.172)	0.173 (0.198)	0.006 (0.963)	0.205 (0.127)
Verbal fluency phonemic	0.166 (0.216)	0.110 (0.414)	0.202 (0.132)	0.103 (0.445)	0.141 (0.295)

Data are presented as correlation coefficients (*p*-values).
BNT: Boston Naming Test, MMSE: Mini-Mental State Examination, RNFL: retinal-nerve-fiber layer, SVLT: Seoul Verbal-Learning test.

thickness and Mini-Mental State Examination (MMSE) and/or cognitive subdomain scores (**Table 1**). The univariate-linear-regression analysis did not find a significant correlation after adjusting for age, education years, and sex (data not shown).

The results support previous studies that have also shown the absence of correlation between these parameters. In contrast, many studies have identified a significant correlation between the reduction of RNFL thickness and the severity of cognitive impairment in patients with MCI and AD.[2,3] Interestingly, 2 studies reported an inverse relationship between RNFL thickness and cognitive function in patients with MCI.[6,7] Knoll et al.[7] have suggested that gliotic reactive changes preceded the loss of neurons and resulted in thicker RNFL in MCI patients than in controls.

Previous studies have shown the accumulation of Aβ in the RNFL, the ganglion-cell layer (GCL), the inner plexiform layer, and the inner nuclear layer of the retina. The accumulation of Aβ in the GCL occurs early in the course of neurodegeneration caused by AD[8] and leads to microglial activation and disruption of retinal architecture. The timeline of accumulation of Aβ plaques in the retinal structures suggests that RNFL thickness may be observed in the later stages of the disease.[9] The pathologic changes associated with Aβ in RNFL may be less pronounced in MCI patients due to the reduced impact of the disease on cognitive impairment. Interestingly, Iseri et al.[10] identified a significant decrease in macular volume, which was negatively correlated with the MMSE score but not with RNFL thickness. This suggests that macular volume may be a better predictor of cognitive impairment than RNFL thickness.

This study has several limitations that should be considered. First, the sample size is small, and the study was conducted in a single center with patients of only one ethnicity. Second, the study only evaluated RNFL thickness, and not macular volume or GCL thickness.

In conclusion, this study did not find an association between RNFL thickness and cognitive function in MCI patients. Further studies are required to clarify the relationship of RNFL thickness and disease severity in early-stage of AD.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Ophthalmological data of the participants

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Supplementary Fig. 1

OCT. OCT image of fundus (A). The RNFL thickness measured in the study was shown (arrow) (B), and the measured value throughout 360° was analyzed for comparison with the average values (C).

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