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Associations Between Retinal Nerve Fiber Layer and Ganglion Cell Layer in Middle Age and Cognition From Childhood to Adulthood

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IMPORTANCE The retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) have been proposed as potential biomarkers for Alzheimer disease (AD). Although a number of studies have shown that knowing the thickness of RNFL and GCL can help differentiate between patients with AD and healthy controls, it is unclear whether these associations are observable earlier in life.

OBJECTIVE To examine whether RNFL and GCL thickness was associated with global cognitive performance in middle age and in childhood and with a decline in cognitive performance from childhood to adulthood and whether RNFL and GCL thickness was associated with decline in specific cognitive domains over the same period.

DESIGN, SETTING, AND PARTICIPANTS This longitudinal cohort study involved members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal representative birth cohort from New Zealand (n = 1037). Participants were born in 1972 to 1973 and followed up until age 45 years, with 94% of the living cohort still participating.

MAIN OUTCOMES AND MEASURES Cognitive performance (Full Scale IQ, processing speed, perceptual reasoning, and verbal comprehension) measured at ages 7, 9, and 11 years (mean value) and age 45 years, and RNFL and GCL thickness measured via optical coherence tomography (OCT) at age 45 years.

RESULTS Data were analyzed between August 2020 and April 2021. Data from 865 participants were included in the present study (50.2% male, 49.8% female; 92.2% of the 938 study members seen at age 45 years). Of the 73 participants who were excluded, 63 were excluded because of issues with OCT scans and 10 were excluded because of diseases affecting the retina. Thinner RNFL and GCL were associated with lower Full Scale IQ in childhood and at age 45 years. Thinner RNFL was also associated with a greater decline in processing speed from childhood to adulthood.

CONCLUSIONS AND RELEVANCE RNFL and GCL thickness in middle age was associated with cognitive performance in childhood and adulthood, and thinner RNFL with a decline in processing speed between childhood and adulthood. These data emphasize the potential utility of OCT measures as biomarkers of cognitive function; however, further longitudinal studies are needed to determine whether retinal thinning precedes cognitive decline and whether other confounding factors may account for this association.

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Supplemental content

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Identifying people at risk of Alzheimer disease (AD) as early as possible is important for optimizing disease management, but distinguishing early pathological cognitive changes from normal cognitive aging is difficult. The global prevalence of AD is increasing, as are the associated human toll and economic burden.[1] Given the failure of clinical trials to treat advanced AD, research focus has moved to identifying people in the preclinical stage, where intervention may be more effective.[2] The preclinical stage may begin long before symptoms reach a diagnostic threshold,[3] with neurostructural changes indicating the trajectory of preclinical AD diverges from the normal cognitive aging trajectory decades before diagnosis.[4] Alzheimer disease is typically diagnosed based on clinical assessment of symptoms, meaning that the disease has to be sufficiently advanced for it to be distinguished from age-related cognitive decline.[5] However, this level of symptomology indicates significant and irreversible damage has already occurred.[6,7]

The retina shows promise as a biomarker of AD because it shares many characteristics with the brain.[8,9] It is part of the central nervous system, it shares a similar embryological and developmental pathway to the brain, and retinal ganglion cells synapse directly on the brain.[10] The retina also has the advantage of being easily and noninvasively imaged using optical coherence tomography (OCT).[11] In this relatively new field, research has shown that the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) are thinner in individuals with AD and mild cognitive impairment,[12-14] although the evidence of retinal thinning in preclinical AD is mixed.[15-24] It is unclear at which stage in the disease process differences in RNFL or GCL thickness become apparent in those who will go on to develop AD, vs their normally aging peers.

The temporal order of retinal thinning and cognitive decline is also unclear. Longitudinal studies have suggested that retinal thinning may precede and predict cognitive decline and dementia diagnoses.[15-21,25] One longitudinal study compared cognitive performance in childhood and adulthood and reported findings that were contrary to other studies (ie, thicker RNFL was associated with poorer functioning).[26] Deterioration of cognitive functioning begins insidiously and gradually years before diagnosis with AD.[27] While many studies tend to use standard clinical assessment tests, such as the Mini-Mental State Examination or Montreal Cognitive Assessment, they may not be particularly effective at detecting people in the early stages of cognitive decline.[28,29] Few studies include comprehensive neuropsychological testing across a range of cognitive domains, although evidence suggests that some domains may be more noticeably affected in early cognitive decline.[30]

Repeated cognitive assessments across the life course would allow us to quantify intraindividual cognitive change, providing a more nuanced picture of cognitive aging and its relationship to RNFL and GCL thickness. Therefore, the aim of our study was to first examine whether RNFL and GCL were associated with global cognitive performance cross-sectionally in middle age (age 45 years) and in childhood. Second, we investigated whether RNFL and GCL were associated with change in IQ from childhood to adulthood, hypothesizing that people showing cognitive deterioration (ie, a decrease in cognitive performance across the life course, indicating increased risk for AD[31]) would also have thinner RNFL and GCL. Our third objective was to investigate whether decline in specific cognitive abilities was associated with RNFL and GCL thickness at age 45 years. We hypothesized that measures of fluid intelligence (ie, perceptual reasoning and processing speed) would be more sensitive to cognitive decline than a measure of crystallized intelligence (verbal comprehension) in our middle-aged cohort, and therefore that change in perceptual reasoning and processing speed would be associated with RNFL and GCL thickness.

Key Points

Question Is the thickness of the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) in middle age associated with cognitive function and decline from childhood to adulthood?

Findings In this cohort study, thinner RNFL and GCL in middle age were associated with lower global cognition scores in childhood and at age 45 years, but not with global cognitive decline from childhood to adulthood. Thinner RNFL in middle age was associated with greater decline in processing speed from childhood to adulthood.

Meaning RNFL may be a useful biomarker of early cognitive decline, but further longitudinal studies are needed to determine whether retinal thinning precedes cognitive decline.

Methods

Participants

Participants were members of the Dunedin Multidisciplinary Health and Development Study, a representative birth cohort (n = 1037; 91% of eligible births, 51.6% male) born between April 1, 1972, and March 31, 1973, in New Zealand. The cohort represents the full range of socioeconomic status in the general population of New Zealand and is predominantly New Zealand European/Pākehā (93%). The study design and participant characteristics have been described extensively elsewhere.[32] Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years, and most recently at age 45 years (2017-2019), when 94% of the 997 living study members participated. The Otago Ethics Committee approved each phase of the study, and written informed consent was obtained from all study members. Study members were offered a small reimbursement for their time and travel expenses.

Optical Coherence Tomography

Optical coherence tomography measurements were taken at age 45 years. Scans were performed in the morning by trained technicians using a spectral-domain OCT machine (Cirrus HD-OCT, model 5000; Carl Zeiss Meditec). Measurements calculated were mean RNFL thickness and thickness of 4 quadrants (superior, temporal, inferior, and nasal) and mean thickness of ganglion cell–inner plexiform layer (GCIPL, abbreviated as GCL) and thickness of 6 segments (temporal-superior,

superior, nasal-superior, nasal-inferior, inferior, and temporal-inferior). Sample scans of each layer are shown in eFigure 1 and eFigure 2 in the Supplement.

Trained graders checked all scans for quality. Scans were removed from the final data set if there were OCT machine problems (eg, signal strength below 6, scan not correctly positioned, scan inverted, or image artifacts). Data for 7 study members were removed because they had diseases affecting the retina (multiple sclerosis, retinitis pigmentosa, brain tumors, diabetic laser pan-retinal photocoagulation, and an anomalous optic nerve head). Nine study members were assessed by 2 ophthalmologists as having glaucoma; data for glaucomatous eyes were removed from the data set, and nonglaucomatous eye data were retained. When data from 1 eye were available, that eye was used; when both eyes were available, the mean of the measurements from both eyes was used.

Cognitive Testing

Cognitive function was assessed in childhood at ages 7, 9, and 11 years and in adulthood at age 45 years. All tests were administered by trained health professionals according to standard protocols. IQ scores were from the Wechsler Intelligence Scale for Children–Revised (WISC-R)[33] and the Wechsler Adult Intelligence Scale (WAIS-IV),[34] both standardized to mean (SD) of 100 (15). A mean was calculated for the childhood IQ scores across the 3 time points because of the labile nature of IQ measurements in childhood.[35] Full Scale IQ (FSIQ) is a measurement of global cognition derived from all subtests of the WISC-R or WAIS-IV. Three indexes from the WISC-R and WAIS-IV were used, each measuring a specific cognitive domain: verbal comprehension (VCI), perceptual reasoning (PRI), and processing speed (PSI). These indexes were calculated according to the test manual. Full details of these tests are available in the eMethods in the Supplement.[36]

Cognitive decline from childhood (mean values from ages 7, 9, and 11 years) to adulthood (age 45 years) in FSIQ and specific domains was calculated using a statistical adjustment approach, where a residualized change score was calculated by measuring the deviation in a participant's actual adult score from the adult score that was predicted based on their childhood score, as previously reported.[37] Negative scores indicated cognitive decline.

Data Analysis and Statistics

Analyses were conducted in SPSS version 26 (IBM Corp) between August 2020 and April 2021. Multivariable linear regression models were used to test whether cognitive functioning was associated with RNFL and GCL thickness. Regression models were first constructed with FSIQ, a measure of global cognition. Next, regression analysis was repeated with change in cognitive domains as predictors. Because of high correlations between RNFL and GCL variables, we ran separate regression models for each retinal measure. All models were adjusted for sex, intraocular pressure, axial length, and optic disc size (the eMethods in the Supplement provide details of these variables). All *P* values were 2-sided, and *P* values were not adjusted for multiple analyses. Analyses were checked for reproducibility by an independent statistician, who recreated the code and output using the manuscript and an unaltered copy of the data set. Although retinal thickness declines with age,[38] all participants were chronologically the same age, so age was not included as a covariate in any models. Reporting guidelines from Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were followed.

Results

The final data set was determined from those study members with RNFL data available (n = 865; female, n = 431 [49.8%]; male, n = 434 [50.2%]) for analyses using RNFL variables, and for those study members with GCL data available (n = 861; female, n = 430 [49.9%]; male, n = 431 [50.1%]) for analyses using GCL variables.

Attrition analysis revealed that participants whose OCT data were excluded at age 45 years (because of issues with the scan or diseases affecting the retina) had slightly lower childhood FSIQ (OCT included: mean [SD] FSIQ, 101.3 [13.8]; OCT excluded: mean [SD] FSIQ, 95.7 [20.9]; $t_{67.1} = 2.14$; $P = .04$). There were no differences in childhood socioeconomic status as measured with a 6-point scale (OCT included: mean [SD], 3.8 [1.1]; OCT excluded: mean [SD], 3.8 [1.2]; $t_{74.8} = -0.2$, $P = .84$). (Details about the scale are in the eMethods in the Supplement.)

The range of residualized FSIQ change was −39.92 to 31.54, and negative residualized FSIQ change scores were recorded for 50.5% of participants, indicating that many study members were experiencing at least some cognitive decline by age 45 years.

Adult Global Cognition

At age 45 years, lower FSIQ was associated with thinner mean RNFL thickness ($B = 0.202$, $P < .001$), as well as thinner nasal quadrant ($B = 0.118$, $P = .01$), and inferior quadrant ($B = 0.115$, $P = .001$) (**Table 1**).

Lower FSIQ at age 45 years was also associated with thinner mean GCL thickness ($B = 0.178$, $P = .04$), as well as thinner temporal-superior segment ($B = 0.216$, $P = .01$), inferior segment ($B = 0.187$, $P = .02$), and temporal-inferior segment ($B = 0.224$, $P = .008$) (Table 1).

Childhood Global Cognition

Lower childhood FSIQ was associated with thinner mean RNFL at age 45 years ($B = 0.213$, $P < .001$), as well as thinner RNFL in the nasal quadrant ($B = 0.117$, $P = .008$), and inferior quadrant ($B = 0.140$, $P < .001$) (Table 1).

Lower childhood FSIQ was associated with thinner mean GCL thickness ($B = 0.247$, $P = .003$), as well as thinner GCL in the temporal-superior ($B = 0.255$, $P = .001$), superior ($B = 0.201$, $P = .01$), nasal-superior ($B = 0.169$, $P = .03$), nasal-inferior ($B = 0.191$, $P = .01$), inferior ($B = 0.221$, $P = .003$), and temporal-inferior segments ($B = 0.271$, $P = .001$).

Global Cognitive Decline

Linear regression controlling for sex and ocular covariates revealed no statistically significant association between re-

Table 1. Associations Between Full Scale IQ at Age 45 Years, Mean Childhood Full Scale IQ (Ages 7, 9, and 11 Years), and Residualized Change in Full Scale IQ With RNFL and GCL Thickness[a]

	Adult IQ		Child IQ		Residualized IQ change	
	B (95% CI)	*P* value	*B* (95% CI)	*P* value	*B* (95% CI)	*P* value
RNFL						
Mean	0.202 (0.089 to 0.315)	<.001[b]	0.213 (0.108 to 0.318)	<.001[b]	0.019 (−0.055 to 0.094)	.61
Temporal	0.075 (−0.024 to 0.174)	.14	0.075 (−0.017 to 0.167)	.11	0.012 (−0.053 to 0.077)	.71
Superior	0.070 (0.000 to 0.140)	.05	0.058 (−0.007 to 0.123)	.08	0.017 (−0.029 to 0.063)	.46
Nasal	0.118 (0.024 to 0.211)	.01[c]	0.117 (0.030 to 0.230)	.008[d]	0.017 (−0.045 to 0.078)	.59
Inferior	0.115 (0.050 to 0.180)	.001[d]	0.140 (0.080 to 0.200)	<.001[b]	−0.003 (−0.046 to 0.040)	.87
GCL						
Mean	0.178 (0.005 to 0.351)	.04[c]	0.247 (0.087 to 0.406)	.003[d]	−0.018 (−0.132 to 0.097)	.76
Temporal-superior	0.216 (0.047 to 0.385)	.01[c]	0.255 (0.099 to 0.411)	.001[d]	0.009 (−0.103 to 0.121)	.88
Superior	0.146 (−0.019 to 0.311)	.08	0.201 (0.048 to 0.354)	.01[c]	−0.007 (−0.117 to 0.102)	.89
Nasal-superior	0.073 (−0.088 to 0.234)	.37	0.169 (0.020 to 0.317)	.03[c]	−0.054 (−0.161 to 0.052)	.32
Nasal-inferior	0.113 (−0.050 to 0.275)	.17	0.191 (0.041 to 0.341)	.01[c]	−0.036 (−0.143 to 0.071)	.51
Inferior	0.187 (0.027 to 0.347)	.02[c]	0.221 (0.074 to 0.369)	.003[d]	0.007 (−0.098 to 0.113)	.89
Temporal-inferior	0.224 (0.059 to 0.389)	.008[d]	0.271 (0.118 to 0.423)	.001[d]	0.001 (−0.109 to 0.111)	.99

Abbreviations: GCL, ganglion cell layer; RNFL, retinal nerve fiber layer.

[a] Models were adjusted for sex, intraocular pressure, axial length, and optic disc area.

[b] $P < .001$.

[c] $P < .05$.

[d] $P < .01$.

sidualized change in FSIQ and any RNFL or GCL measurements (all $P > .05$, Table 1).

Decline in Cognitive Domains

Reduction in processing speed was associated with thinner mean RNFL thickness ($B = 0.292$, $P = .04$), and thinner RNFL in the temporal ($B = 0.403$, $P = .01$) and inferior quadrants ($B = 0.590$, $P = .02$) (**Table 2**). Reduction in verbal comprehension or perceptual reasoning was not associated with any measure of RNFL or GCL.

Discussion

We found that RNFL and GCL at age 45 years were associated with FSIQ in adulthood and in childhood. Neither RNFL nor GCL thickness was associated with a decline in global cognitive performance over time. However, thinner overall RNFL in middle age was associated with a decline in processing speed from childhood to adulthood, but not with a decline in perceptual reasoning over the same time frame.

These findings suggest that the retina is a biological correlate of cognitive functioning. It has been repeatedly observed that people with higher IQs tend to live longer and be healthier than those with lower IQs, but the mechanisms for this association are likely to be multifarious and complex.[39,40] Our findings suggest that RNFL could be an indicator of overall brain health and that IQ may reflect a healthy and well-functioning brain. This finding may also lend support to the cognitive reserve hypothesis: that people with higher intelligence or more education retain a higher level of functioning for longer despite brain pathology.[41]

Although global cognitive decline was evident in this middle-aged sample, this decline did not appear to be reflected in RNFL or GCL thickness. As measures of fluid intelligence are thought to be more sensitive markers of early cognitive decline than measures of crystallized intelligence or global cognition,[27,30,42] we hypothesized that processing speed and perceptual reasoning would be associated with RNFL and GCL thickness. This hypothesis was partly supported, because greater decline in processing speed (but not perceptual reasoning) was associated with thinner RNFL (but not GCL). Consistent with our hypothesis, we observed no association between decline in verbal comprehension, a marker of crystallized intelligence, and RNFL or GCL.

We expected that people in the early stages of cognitive decline would experience deterioration in cognitive performance preferentially in certain cognitive domains, rather than in their global cognitive performance. Processing speed may be particularly sensitive to differences in pathological and normal trajectories, as it is thought to be the first cognitive domain to show measurable decline in normal cognitive aging,[43] and one of the first domains affected in preclinical AD.[30,44-46] Poor performance on processing speed tasks may predict dementia and functional decline.[47] Consistent with our findings, a recent study found that RNFL thickness was associated with psychomotor speed and visuomotor tracking.[48] Reduced processing speed is associated with white matter pathology,[49] smaller hippocampal volume,[50] and regional cerebral blood flow deficits.[51] These structural and functional correlates of processing speed suggest that declines in processing speed may indicate loss of cerebral integrity associated with AD pathology.

Table 2. RNFL and GCL Thickness With Residualized Change in Verbal Comprehension, Perceptual Reasoning, and Processing Speed From Childhood to Adulthood[a]

	VCI change		PRI change		PSI change	
	B (95% CI)	*P* value	*B* (95% CI)	*P* value	*B* (95% CI)	*P* value
RNFL						
Mean	0.011 (−0.041 to 0.064)	.67	0.111 (−0.168 to 0.390)	.44	0.292 (0.019 to 0.566)	.04[b]
Temporal	0.017 (−0.043 to 0.077)	.58	0.001 (−0.320 to 0.322)	.99	0.403 (0.089 to 0.718)	.01[b]
Superior	0.051 (−0.034 to 0.136)	.24	0.275 (−0.178 to 0.728)	.23	0.157 (−0.288 to 0.602)	.49
Nasal	−0.008 (−0.072 to 0.056)	.80	0.281 (−0.057 to 0.620)	.10	0.015 (−0.318 to 0.348)	.93
Inferior	−0.012 (−0.103 to 0.080)	.80	−0.109 (−0.596 to 0.377)	.66	0.590 (0.114 to 1.066)	.02[b]
GCL						
Mean	−0.007 (−0.042 to 0.028)	.71	0.078 (−0.106 to 0.262)	.40	0.068 (−0.115 to 0.252)	.46
Temporal-superior	−0.008 (−0.028 to 0.044)	.66	0.135 (−0.053 to 0.324)	.16	0.111 (−0.077 to 0.299)	.25
Superior	−0.001 (−0.037 to 0.036)	.97	0.100 (−0.093 to 0.293)	.31	0.076 (−0.117 to 0.268)	.44
Nasal-superior	−0.015 (−0.052 to 0.023)	.44	−0.001 (−0.200 to 0.197)	.99	0.014 (−0.184 to 0.211)	.89
Nasal-inferior	−0.018 (−0.055 to 0.019)	.35	0.021 (−0.175 to 0.217)	.84	0.062 (−0.133 to 0.258)	.53
Inferior	−0.006 (−0.043 to 0.032)	.77	0.085 (−0.115 to 0.284)	.40	0.076 (−0.123 to 0.275)	.45
Temporal-inferior	−0.004 (−0.040 to 0.033)	.85	0.149 (−0.044 to 0.341)	.13	0.074 (−0.118 to 0.266)	.45

Abbreviations: GCL, ganglion cell layer; PRI, perceptual reasoning index; PSI, processing speed index; RNFL, retinal nerve fiber layer; VCI, verbal comprehension index.

[a] Models were adjusted for sex, intraocular pressure, axial length, and optic disc area.

[b] $P < .05$.

The finding that RNFL was associated with processing speed, but GCL was associated with global cognitive functioning only, was not wholly unexpected. Thinner GCL has been associated with prevalent dementia, but thinner RNFL was associated with greater risk of incident dementia in the Rotterdam Study,[16] suggesting that RNFL thinning occurs prior to the clinical manifestations of dementia, while GCL thinning becomes apparent after symptoms have progressed beyond a clinical threshold. However, the pattern of retinal thinning is not clear.[52] Longitudinal studies with repeated OCT and cognitive assessments in the decades prior to any potential AD diagnosis could potentially elucidate whether retinal thinning precedes cognitive decline.

It is unclear when measurable cognitive decline begins in AD, and it could be that cognitive differences between normal cognitive aging and those who will go on to develop AD were not yet detectable. It is also possible that the cognitive change we have detected was not related to or predictive of AD. A number of explanations for retinal thinning and cognitive decline in middle age do not presupposethe person will go on to develop AD, including substance/alcohol abuse, traumatic brain injury, and neurodegenerative diseases such as Parkinson disease.[53,54] These explanations do not preclude the presence of other confounding variables. Because this is a population-based birth cohort, we did not exclude any participants on the basis of health status, except for those with diseases directly affecting the retinal layers.

Strengths and Limitations

A particular strength of this study is the battery of neuropsychological tests that were used. Many studies use short dementia screening tests, such as the Mini-Mental State Examination or Montreal Cognitive Assessment, which have ceiling effects in a healthy population and cannot provide a nuanced picture of the amount and type of change observed longitudinally.[29] In the earliest stages of preclinical AD, more specific cognitive tests may be required to detect differences within a population. A limitation of the study is that OCT measurements were conducted at one time point only (age 45 years). It is possible that retinal thinning over time is a better predictor of AD than retinal thickness at a single point in time.

Conclusions

To summarize, our study used a unique life-course approach to show that RNFL, and to a lesser extent GCL, in middle age may reflect lifelong interindividual differences in global cognition. In addition, RNFL may be particularly sensitive to changes in processing speed by middle age. RNFL thinning could be a useful biomarker in identifying those experiencing the early stages of cognitive decline, before global cognitive decline becomes apparent. However, further longitudinal studies are required to elucidate whether retinal thinning predicts AD.

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Author Contributions: Dr Barrett-Young had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Barrett-Young, Tham, Wong, Poulton.
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