ORIGINAL RESEARCH

Relationships Among Retinal Nerve Fiber Layer Thickness, Vascular Endothelial Growth Factor, and Cognitive Impairment in Patients with Schizophrenia

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Background: Studies have suggested retinal nerve fiber layer (RNFL) involvement in the pathogenesis of schizophrenia. Additionally, research has shown that vascular endothelial growth factor (VEGF) potentially contributes to the pathophysiology of psychiatric disorders. Therefore, this study aimed to investigate VEGF, RNFL, and correlations with cognitive impairments in schizophrenia patients.

Methods: Patients with schizophrenia (n = 138) were compared to healthy controls (n = 160). RNFLs were measured with optical coherence tomography (OCT). The Stroop color and word test (SCWT) was used to evaluate neurocognition. Blood samples were collected to measure VEGF. SPSS 20.0 was used to perform analysis of covariance, t-tests, partial correlation analysis, and linear regression.

Results: Thinner RNFLs were found in schizophrenia patients ($p < 0.001$). RNFL showed a significant correlation with SCWT scores (all $p < 0.05$). Serum level of VEGF was lower in patients with schizophrenia ($p = 0.010$). Total and inferior RNFL thicknesses of right eyes were positively correlated to VEGF level (RNFL total thickness $p = 0.032$, inferior thickness $p = 0.014$).Total RNFL thicknesses were shown to be reduced following a prolonged duration of illness (both p < 0.01).

Conclusion: These findings suggest that patients with schizophrenia have degeneration with RNFL thickness following illness duration, which may contribute to neurocognitive impairments observed in schizophrenia. VEGF is speculated to play some important role on RNFL degeneration with schizophrenia patients.

Keywords: RNFL, VEGF, cognitive impairment, schizophrenia

Introduction

Neurodegeneration of the brain may pertain to a variety of functional deficits that are essential features of the schizophrenia.[1] The visual nervous system in the brain primarily originates from the neuroectoderm. Retinal anomalies also present in schizophrenia patients,[2] including atrophy of retinal nerve fiber layers (RNFL).[3–5] The thickness decrease observed in the RNFL could reflect retinal cell loss.[6]

Studies have shown both structural and functional deficiency in the visual afferent pathways of patients with schizophrenia.[7,8] For example, inherent connectivity of the primary afferent visual pathway has been found to be reduced in schizophrenia patients, and impaired visual object perception is considered

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a pathogenic risk factor of schizophrenia.[9] Deviation in the process of visual information transmission is more common in schizophrenia patients.[10] The retina as the starting station of the visual pathway through the brain is an especially accessible substrate for investigating the brain pathology of schizophrenia.[11] In vivo visualization of the retina can be achieved by optical coherence tomography (OCT), a non-invasive, fast imaging technique.[10]

Serum vascular endothelial growth factor (VEGF) has been shown to provide protection in the inflammatory process of schizophrenia.[12] Kurihara et al reveal an essential role of VEGF in maintaining choroid vasculature and cone photoreceptors, critical for central and color vision.[13] However, the effect of VEGF on the RNFL of schizophrenia patients remains unknown.

The Stroop color-word test (SCWT) is widely utilized as a measurement of neurocognition, which is thought to reflect frontal lobe function. The Stroop paradigm requires an intact visual system, especially color vision and visual acuity.[14] While neuropsychology textbooks warn that visual dysfunction may interfere with Stroop performance,[15] how the retina affects the visual-related cognitive impairment observed in schizophrenia remains unknown.

We conducted this study to investigate structural changes in the retina of individuals with schizophrenia and its correlations with cognitive performance, as assessed by the SCWT. We predicted that patients with schizophrenia would show reduced RNFL thickness, and that would be associated with visual cognitive impairments under the imbalanced level of VEGF.

Methods and Materials
Recruitment of Subjects

This cross-sectional study enrolled patients with schizophrenia and healthy controls aged 18–60 years. The present study was conducted from July 2018 to January 2020. Two experienced psychiatrists confirmed the diagnosis of schizophrenia based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (Structured clinical interview for diagnosis-I version, SCID-I). All patients had been receiving stable doses of antipsychotic drugs for at least three months before entry into the study. We recorded smoking status as an interfering factor considering the influence of smoking on cognition and the retina.[16,17] Healthy controls recruited from voluntary hospital staff were also evaluated

by SCID-I to rule out Axis I disorders. All participants fulfilled the exclusion criteria and were free of central nervous system diseases, head trauma, hypertension, diabetes mellitus, drug/alcohol abuse or addiction, glaucoma, cataract, high astigmatism (sphere dpt [diopter] > 4 and cylinder dpt > 2), high myopia (>6.0 diopters), visual field defect, optic media opacities, chromatodysopia, or other significant medical illnesses (eg, cancer, ongoing infection). The best corrected visual acuity and body mass index (BMI) were also recorded. Due to the particularity of the condition of schizophrenic patients, guardians need to supervise and drive on behalf of their behavioral ability. Especially during the development of acute symptoms. All subjects or guardians provided written informed consent. Our study complies with the Declaration of Helsinki. The project was approved by the Institutional Review Board of Beijing Huilongguan Hospital (number 2018–33).[18]

Psychological Evaluation

The SCWT was used to evaluate the word/color processing speed and visual cognitive flexibility in all subjects.[19] The SCWT features a three-page test booklet. The first page consists of the words "red," "yellow," and "blue" printed in black ink; the second page consists of columns of circles printed in red, yellow, or blue ink; and the third page consists of the words "red," "yellow," and "blue" printed in red, yellow, or blue ink, but the words and printed colors never match. Subjects were required to read the words and/or name the color on each page.[20] The SCWT includes four direct scores, based on the time of items correctly completed on each of the three stimulus sheets (word reading time [WRT], color naming time [CRT], color-word reading time [CWRT]; and word-color naming time, [WCRT] was recorded).

The Positive and Negative Syndrome Scale (PANSS) assessment was performed on subjects with schizophrenia. This scale was designed and standardized to assess the presence and severity of different types of schizophrenia symptoms.

The PANSS consists of 7 positive scale items, 7 negative scale items, and 16 general psychopathology scale items, resulting in 30 total items to assess symptoms of schizophrenia. Three additional supplementary items are added to assess the risk of aggression. This study was evaluated by two psychiatrists who were blind to the study design and grouping. The kappa value of the consistency test was 0.85.[21]

Measurement of RNFL with OCT

The best corrected visual acuity of each eye was measured via Snellen visual acuity. An anterior slit lamp microscope and Goldman tonometer were used to exclude eye diseases and measure intraocular pressure. Ophthalmologists used a 90D focusing lens for fundus examination to observe and exclude diseases of the RNFL or the macula around the disc. OCT 2002 type (Topcon, Japan) was used to scan both eyes (see Figure 1). Optic data were obtained with an OCT raster centered tu the optic nerve head in the "6 mm × 6 mm" cube with a 512×218 scan and 200 pixels. The macular region was scanned in a radial "6 mm × 6 mm" region at 1024×12 and 200 superpixels. OCT software (version 8.42) automatically focused on the center of the disc or macular region then extracted a circle with a diameter of 3–4 mm to measure the RNFL thickness. RNFL thickness was measured at the 12 clock positions and in the four 90°quadrants of the whole eyeball, including the superior, inferior, nasal and temporal quadrants. All data of retina were all automatically calculated by OCT All the above ophthalmic methods and data were recorded as described in our earlier studies.[18]

Blood Sample Tests

Serum samples were collected by nurses following fast (6:30 am). Blood was naturally coagulated at room temperature for 10–20 minutes, centrifuged for approximately 10 minutes (3000 rpm), and then the serum was separated, rapidly frozen, and stored at −80°C until analysis.VEGF levels in serum were determined with enzyme-linked immunosorbent assay (ELISA) kits (Abcam, USA) by two technicians who were blinded to the status of the subjects. The absorbance (OD value) was measured at 450 nm by a microplate reader, and the concentration of VEGF was calculated by a standard curve. Interassay variances were below 8%. The detection limit of the assay was 9 pg/mL. Additionally, each serum sample was assayed in duplicate for glucose, triglyceride, and cholesterol, as reported earlier.[18]

Statistical Analysis

Data were analyzed with SPSS 20.0 software. A Shapiro–Wilk test was used to verify whether the data followed a normal distribution. Independent t-tests and Chi-square tests were used to compare the demographic and clinical data between patients and normal controls. Analysis of covariance (ANCOVA) was also used to compare the two groups, after controlling for age, sex, and smoking. Partial correlation analysis was used to assess the correlations between RNFL thickness and SCWT of the participants, controlling for age, sex, and smoking. Multiple linear regression analysis was used only in the schizophrenia patients. Age of onset, VEGF and duration of illness were set as independent variables and RNFL thickness of both eyes was set as dependent variables, after controlling for sex education and smoking. Total RNFL thickness, cup volume and average macular thickness were set as independent variables, scores of PANSS and Stroop test were
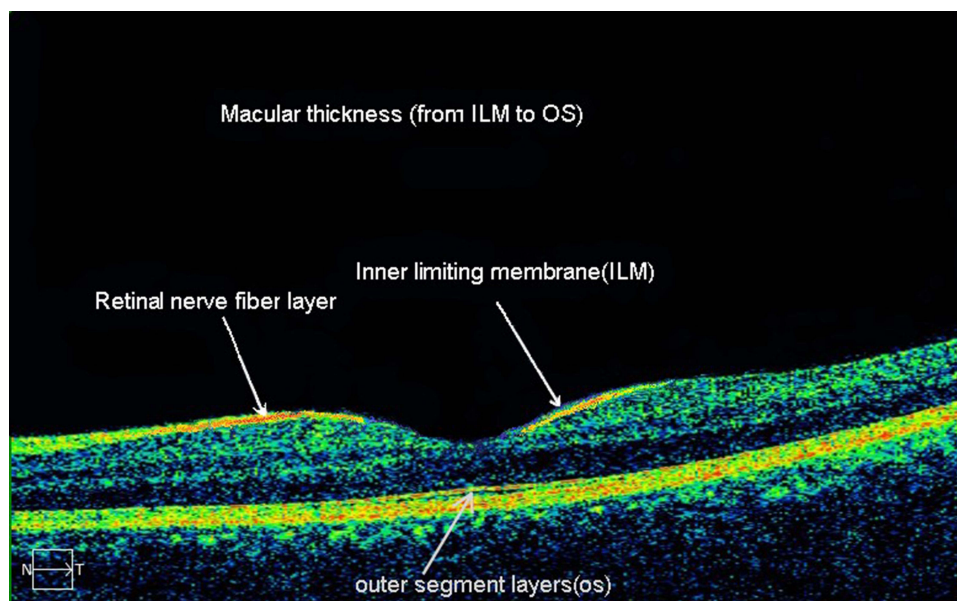
Figure 1 Retinal nerve fiber layer of OCT.

set as the dependent variable, after controlling for age, sex and smoking. A p-value < 0.05 for a two-tailed test was considered statistically significant.

Results

A total of 138 patients with schizophrenia and 160 healthy controls were enrolled in our study. As shown in Table 1, we found significant differences in age (p = 0.007), sex (p = 0.001), and smoking condition (p < 0.001) between the patients and normal controls, while there were no significant differences in BMI or years of education between the two groups. The level of VEGF was lower in patients with schizophrenia (p = 0.010). Neurocognition, as assessed via the SCWT, was significantly impaired in the schizophrenia group (all p < 0.05). The schizophrenia group showed significant delay in color naming time, color word reading time and word color naming time of the SCWT when compared to healthy controls (all p < 0.001).

As shown in Table 2, the RNFL thicknesses of both eyes in schizophrenia patients were thinner than that observed in healthy controls (p < 0.001). By analyzing the relationships between color perception scores and retinal structure in the whole subject, we found slight correlations between the total RNFL and CWRT (right eye: p = 0.018, r = −0.192; left eye: p < 0.001, r = −0.341) as well as between the superior and inferior RNFL part of the SCWT results (Figure 2). In Table 3, cognitive testing scores of schizophrenia patients showed no significant correlations with the total of RNFL thicknesses except the CWRT scores (P = 0.010). There were no significant relationships between cognitive testing scores and the cup volume or average macular thickness (all p > 0.05). Only negative symptoms of PANSS showed minor correlations with total RNFL thicknesses (p = 0.050).

In patients with schizophrenia, the total and inferior RNFL thicknesses of right eyes were shown to be thinner following the decreased VEGF level in schizophrenia (RNFL total thickness p = 0.032 and inferior thickness p = 0.014; see Table 4). Age of onset showed no relationships with all RNFL thickness (all p > 0.05). Interestingly, total RNFL thickness was shown to be reduced following a prolonged duration of illness (right eye: β = −0.992, F = −2.708, p = 0.009; left eye: β = −0.496, F = −2.980, p = 0.004); a result also observed in the superior RNFL (right eye: β = −1.334, F = −2.665, p = 0.010; left eye: β = −0.627, F = −1.676, p = 0.099). However, the inferior RNFL showed no relationship with duration of illness (p > 0.05).

Discussion

As we know, this is the first study for correlations among retinal nerve fiber layer thickness, vascular endothelial growth factor, and cognitive impairment in patients with schizophrenia in Asia. Our cross-sectional study revealed that, compared with healthy controls, RNFL thickness in individuals with schizophrenia exhibits thinner, which may have some relationship with visual cognitive impairment. Furthermore, there appeared to be a relationship between illness duration and total RNFL thickness, but not inferior RNFL thickness. VEGF may play an important role on RNFL degeneration with schizophrenia patients.

RNFL and macular thickness were shown to be thinner in both eyes of patients with schizophrenia, which is consistent with observations in previous research.[22–24] Moreover, following a prolonged illness duration, the RNFL thickness of the patients exhibited, decreased. Our results were consistent with a preclinical study on schizophrenia.[25] All these studies provide evidence for the notion of structural and functional changes in retinal integrity of patients with schizophrenia, which maybe supports the neurodegenerative hypothesis of schizophrenia.[26,27]

It should be noted that there appeared to be a relationship between illness duration and superior RNFL thickness. However, the same relationship was not observed for inferior RNFL thickness. Further, there were differences observed in associations between the left RNFL and Stroop results. The seemingly unbalanced bilateral development of the eyes observed in the current study may be related to the hypothesis of asymmetric brain development in schizophrenia.[28,29]

We did not find significant correlations between cup volume with cognitive impairment in schizophrenia. These results were not consistent with the results of a previous study, which showed increased cup volume and cup-to-disc ratio in patients with schizophrenia who had comorbid diseases, and that the enlargement of cup volume was related to cognitive impairment.[24] There was no apparent correlation between cup volume and cognitive symptoms in the absence of co-morbidity factors, like diabetes and hypertension, in our study. These different results may be due to different methods of measuring cognitive ability and differences in the samples studied.

A study reported a parallel alteration of VEGF serum and cerebrospinal fluid levels in subjects with neurotuberculosis.[30] In our study, serum VEGF levels were lower in patients with schizophrenia than those

Table 1 Participant Demographics and Differences in the SCWT Between Individuals with Schizophrenia and Healthy Controls

Mean ± SD	Schizophrenia Group (n=138)	Control Group (n=160)	t/χ²	p
Age, y	45.09 ± 12.47	41.43 ± 9.50	2.737	0.007*
Age onset, y	23.28 ± 9.63	–		
Sex Female, n	66	106	33.470	0.001*
Male, n	72	54		
Education, y	12.43 ± 2.49	12.70 ± 2.78	0.689	0.492
Duration of illness, y	21.74 ± 13.51	–		
Smokers, n (%)	38(27.53)	8(5.80)	51.164	< 0.001*
BMI (kg/m²)	24.32 ± 4.18	23.40 ± 3.16	1.934	0.054
Eye pressure left (mmHg)	15.38 ± 3.12	15.35 ± 3.04	0.082	0.935
Right (mmHg)	15.29 ± 3.43	15.13 ± 2.75	0.395	0.693
Diopters (D) left eye	3.10 ± 1.71	2.68 ± 1.18	0.856	0.396
Right eye	2.86 ± 1.34	2.98 ± 1.20	−0.269	0.789
SBP[1] (mmHg)	111.38 ± 9.51	110.02 ± 8.96	0.319	0.750
DBP[2] (mmHg)	70.91 ± 5.64	71.97 ± 6.31	−1.475	0.141
Glucose (mmol/L)	5.29 ± 1.44	5.39 ± 1.49	−0.486	0.628
Cholesterol (mmol/L)	4.20 ± 0.96	4.78 ± 0.78	−0.097	< 0.001*
Triglyceride (mmol/L)	1.67 ± 0.89	1.46 ± 0.99	1.654	0.100
VEGF[3] (pg/mL)	960.74 ± 149.80	1032.36 ± 182.31	−2.597	0.008*
Stroop color word test				
Word reading time (WRT, s)	16.00 ± 4.45	13.82 ± 9.52	2.402	0.017
Color naming time (CRT, s)	24.95 ± 9.15	16.04 ± 3.67	10.549	< 0.001*
Color word reading time (CWRT, s)	24.11 ± 10.83	18.12 ± 7.69	5.218	< 0.001*
Word color naming time (WCRT, s)	50.07 ± 18.50	30.08 ± 9.80	11.096	< 0.001*
PANSS Positive symptoms	18.85 ± 7.03	–		
Negative symptoms	22.36 ± 9.00	–		
General symptoms	39.15 ± 18.61	–		
Total scores	80.36 ± 31.84	–		

Notes: 1. Systolic blood pressure, 2. Diastolic blood pressure, 3. VEGF, *:P < 0.05.

observed in healthy controls. It indirectly reflects the lower level of VEGF in the brain of schizophrenia patients. Evidence suggests that VEGF can protect against brain cell loss, blood-brain-barrier dysfunction, spatial memory impairment, and cognitive decline in response to injury and Alzheimer disease.[31,32] VEGF may also affect an improvement of hippocampal function and prefrontal cortex volume in schizophrenia.[33,34] Normal levels of VEGF plays an important role in the unbalanced development of synapses in the brain through the inflammatory process.[11] In our study, VEGF was inferred to have some protective affects against degeneration of the RNFL in the right eyes

Table 2 Differences in RNFL Thickness Between Individuals with Schizophrenia and Healthy Controls

Mean ± SD	Schizophrenia Group	Control Group	t	p	F	p'
Right RNFL						
Total thickness (μm)	84.00 ± 21.27	101.96 ± 13.47	−5.333	<0.001	10.872	0.001*
Superior thickness (μm)	99.51 ± 44.45	121.70 ± 27.45	−4.170	<0.001	7.530	0.007*
Inferior thickness (μm)	105.25 ± 44.13	127.85 ± 24.30	−4.461	<0.001	6.689	0.011*
Disc area (mm²)	2.20 ± 1.35	2.32 ± 0.51	−0.803	0.423	0.048	0.995
Cup volume (mm³)	0.12 ± 0.14	0.12 ± 0.13	0.267	0.790	0.561	0.455
Left RNFL (μm)						
Total thickness (μm)	93.64 ± 13.69	105.36 ± 10.81	−6.113	<0.001	33.130	<0.001*
Superior thickness (μm)	117.84 ± 29.03	131.80 ± 19.87	−3.784	<0.001	28.546	<0.001*
Inferior thickness (μm)	120.84 ± 23.64	135.50 ± 16.44	−4.851	<0.001	9.838	0.002*
Disc area (mm²)	2.13 ± 0.91	2.26 ± 0.43	−1.295	0.197	0.099	0.753
Cup volume (mm³)	0.17 ± 0.15	0.12 ± 0.12	2.026	0.044	0.633	0.427
Right macula (μm)						
Average thickness	257.40 ± 39.23	263.44 ± 36.88	−1.244	0.215	0.716	0.475
Central thickness	220.53 ± 39.34	222.98 ± 20.31	−0.592	0.555	1.184	0.238
Inner superior	284.27 ± 45.56	302.85 ± 18.73	−0.401	<0.001	4.755	<0.001*
Inner inferior	274.23 ± 47.36	290.68 ± 20.75	−3.388	0.001	3.524	0.001*
Inner nasal	286.79 ± 46.46	298.22 ± 26.10	−2.428	0.016	1.847	0.066
Inner temporal	268.35 ± 42.93	282.10 ± 19.17	−3.338	0.001	3.378	0.001*
Outer ring superior	254.95 ± 40.25	266.67 ± 20.44	−2.778	0.006	3.542	<0.001*
Outer inferior	245.72 ± 40.98	256.02 ± 19.62	−2.421	0.017	2.776	0.006*
Outer nasal	267.80 ± 42.71	278.16 ± 26.23	−2.331	0.021	2.615	0.010*
Outer temporal	241.59 ± 38.51	247.07 ± 21.43	−1.409	0.160	2.573	0.011*
Left macula (μm)						
Average thickness	254.35 ± 39.50	262.86 ± 47.64	−1.499	0.135	0.614	0.540
Central thickness	219.54 ± 38.41	228.44 ± 25.56	−2.154	0.032	1.223	0.222
Inner superior	280.48 ± 44.58	303.05 ± 16.78	−5.003	<0.001	3.701	<0.001*
Inner inferior	273.43 ± 44.14	292.46 ± 22.35	−4.091	<0.001	2.989	0.003*
Inner nasal	281.17 ± 48.03	296.80 ± 40.59	−2.754	0.006	1.933	0.055
Inner temporal	269.50 ± 44.58	287.66 ± 16.78	−4.027	<0.001	2.915	0.004*
Outer ring superior	252.28 ± 40.14	267.93 ± 16.99	−3.803	<0.001	2.517	0.013*
Outer inferior	242.29 ± 39.12	256.43 ± 16.45	−3.529	0.001	1.606	0.110
Outer nasal	266.74 ± 44.96	284.74 ± 17.62	−3.942	<0.001	1.879	0.062
Outer temporal	238.50 ± 39.11	249.81 ± 15.75	−2.842	0.005	1.182	0.239

Notes: p: for t-test; p': adjusted p for analysis of covariance after controlling for age, sex, and smoking. *:P<0.05.
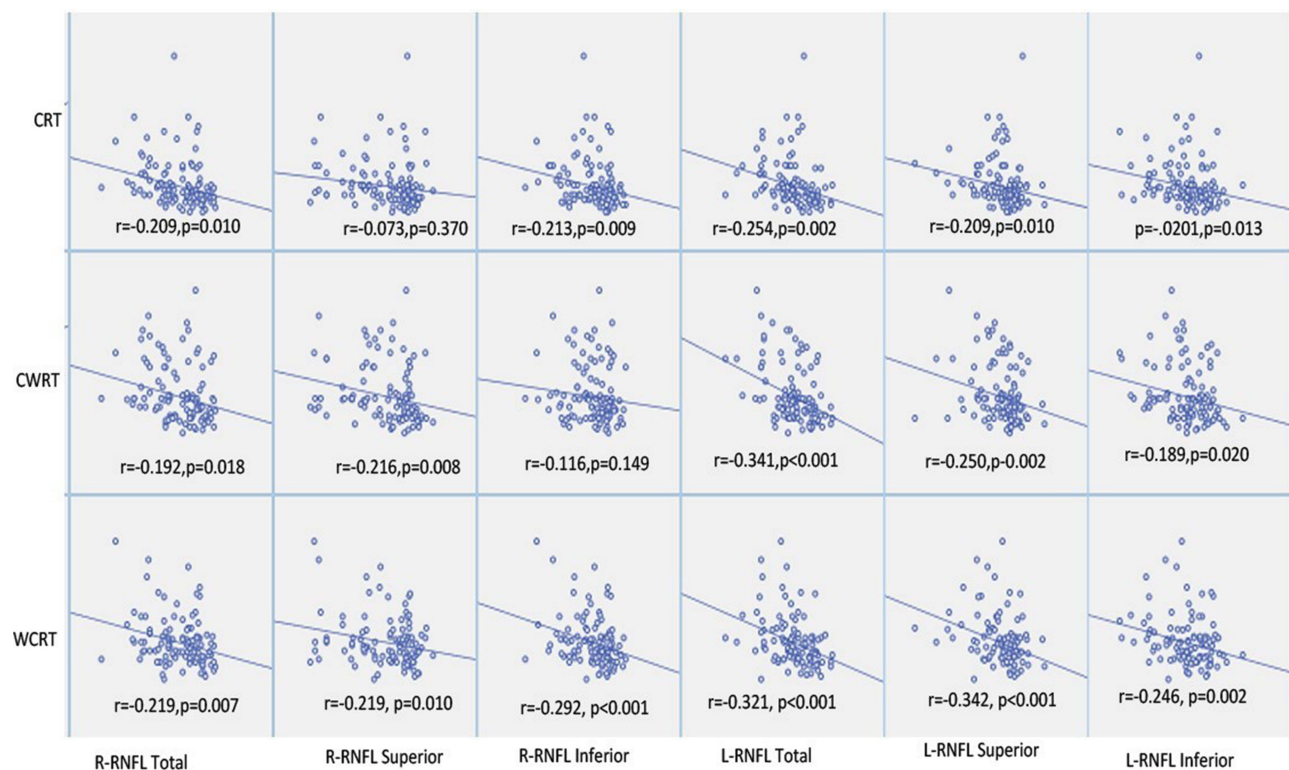
Figure 2 The relationship between the thickness of retinal nerve fiber layer (RNFL) and the scores of the Stroop test.
Abbreviations: R-RNFL, right RNFL; L-RNFL, left RNFL; CRT, color reading time; CWRT, color word reading time; WCRT, word-color naming time.

of schizophrenia patients. The effect of VEGF on the RNFL of right eyes is more prominent, which might indirectly reflect more pronounced protective effects on the left cerebral nerve circuit, according to the visual neural transmission pathway. VEGF might also provide multiform diphase regulation in response to impairment of this nerve pathway.Although cross-sectional studies affect the accuracy of speculation, the precise mechanism by which VEGF is related to cognitive impairment and RNFL change in patients with schizophrenia remains to be elucidated.

Various studies have tried to investigate visual perception as a new endophenotype of schizophrenia.[35,36] SCWT, which was designed as a cognitive test assessed via vision, has been widely used to evaluate reading speed, selective attention, and cognitive flexibility.[37] Previous research has shown that time spent in the SCWT is related to visual search and perceptual speed factors.[38] Increased SCWT response time is a common feature of the impaired cognitive function observed in schizophrenia. Accordingly, in the current study, patients with schizophrenia took more time to complete the SCWT, when compared with healthy controls, which is consistent with the results reported by previous studies.[39,40]

Increased SCWT response time as a measure of cognition impairment exhibited a significant relationship with the RNFL thickness in our study. This is consistent with results presented in a previous study, which found that RNFL impairment is related to visuospatial cognitive impairment.[18] The retina is the first structure to receive and process environmental visual information. Some studies infer that visual deficits in schizophrenia patients are related to the parvocellular pathway or are related to the interaction between the magnocellular and parvocellular pathways containing spatial and temporal information processed.[41,42] Both the two pathways originate from different types of retinal ganglion cells (RGCs). RGCs form the retinal nerve that projects for the most part to the visual cortex to generate vision.[43] The association between early visual processing in the retina and cognitive performance in schizophrenia may be close.[42] Changes in the senior visual nerve of the brain may be related to problems with incoming primary visual processing. Therefore, we speculate that, based on the thinner RNFL thickness observed in patients with schizophrenia, the degeneration of the retinal nerve may be associated with visual cognitive impairment. Retinal nerve cell loss reflects the neural

Table 3 Influence of RNFL on the Cognitive Function of Individuals with Schizophrenia (Linear Regression Analysis)*

Stroop Test	Total RNFL					Cup Volume					Average Macular Thickness				
	Constant	β	S.E.	F	p	Constant	β	S.E.	F	p	Constant	β	S.E.	F	p
Color naming time (CRT, s)	33.275	−0.038	0.039	−0.982	0.327	42.515	4.316	6.120	0.705	0.482	40.207	−0.007	0.014	−0.471	0.638
Color word reading time (CWRT, s)	28.531	−0.111	0.043	−2.580	0.010*	36.107	−0.894	6.380	−0.140	0.889	35.927	−0.002	0.016	−0.154	0.878
Word color naming time (WCRT, s)	44.989	−0.092	0.078	−1.180	0.239	52.141	3.783	9.828	0.349	0.728	65.120	−0.004	0.028	−0.135	0.893
PANSS															
Positive symptoms	23.608	−0.100	0.069	−1.447	0.163	−4.038	−2.842	6.720	−0.423	0.678	25.911	0.003	0.019	0.185	0.855
Negative symptoms	39.090	−0.193	0.093	−2.039	0.050	−25.818	−8.063	8.857	−0.910	0.376	12.840	0.012	0.022	0.539	0.596
Total scores	−48.834	−0.226	0.395	−0.571	0.575	−97.040	−7.429	6.375	−0.194	0.849	29.514	0.074	0.081	0.916	0.369

Notes: *Linear regression model with using each score of Stroop or PANSS as a dependent variable while left RNFL variables each were independent variables after controlling age, sex, duration of illness, education, and smoking. P < 0.05.

Table 4 The Influence of VEGF and Illness Duration on RNFL in Individuals with Schizophrenia (Linear Regression Analysis)*

Right RNFL	Vascular Endothelial Growth Factor (VEGF)					Age onset					Duration of Illness				
	Constant	β	S.E.	F	p	Constant	β	S.E.	F	p	Constant	β	S.E.	F	p
Total thickness	−24.833	0.063	0.029	2.192	0.032*	25.450	−0.334	0.516	−0.647	0.520	74.877	−0.992	0.366	−2.708	0.009*
Inferior thickness	−40.418	0.106	0.042	2.528	0.014b*	1.320	−0.525	0.760	−0.691	0.492	−24.257	−0.726	0.539	−1.347	0.183
Superior thickness	1.559	0.053	0.042	1.255	0.214b	128.899	−0.876	0.702	−1.247	0.217	97.816	−1.334	0.501	−2.665	0.010b*
Left RNFL															
Total thickness	92.002	−0.011	0.013	−0.806	0.424b	124.855	−0.128	0.218	−0.588	0.559	93.247	−0.496	0.167	−2.980	0.004b*
Inferior thickness	120.983	−0.005	0.023	−0.197	0.845	115.867	−0.311	0.329	−0.945	0.349	133.859	−0.405	0.373	−1.086	0.282
Superior thickness	117.496	−0.010	0.029	−0.336	0.738	151.696	0.124	0.500	0.248	0.805	135.088	−0.627	0.374	−1.676	0.099

Notes: *Linear regression model using each RNFL and macula alone as a dependent variable, VEGF, age onset and duration of illness as the independent variables after controlling for sex, education, and smoking status; P < 0.05. [a]Sex and smoking as covariates were significant. [b]Sex as a covariate was significant.

network problems in the development of the brain in schizophrenic patients, and thus the cognitive function with visual participation may be steeply impaired. Abnormal reduction of RNFL indirectly reflects the atypical development of brain structure.[4,25] Further, retinal layer abnormalities might be used as a potential biomarker in schizophrenia, due to significant correlations with clinical features and visual function.[23] Whether this change in the retina follows or plays a decisive role in the impairment of the cognitive development remains to be clarified.

Limitations

There are several limitations to consider in the current single-center, cross-sectional study. First, the thickness of the macula obtained with Topcon SD-OCT2002 was not a single-layer ganglion cell thickness; rather it was a cumulative ganglion cell complex owing to the automatic measurement limitation. Second, doses of antipsychotics used by patients in the current study could be a confounding factor, as it is unknown whether these medications affect the RNFL thickness.[2] Third, the RNFL thickness is just one of the factors related to visual acuity. It is possible there could be other eye conditions that were not balanced in the patients. Fourth, healthy controls are taken from the staff of the hospital, this may bias the exclusion diagnosis of axis 1 due to missing anonymity. Additionally, the cross-sectional design of our study seemed to be insufficient speculation about progressive degeneration of RNFL during the course of schizophrenia. Finally, the lack of a control neuroimaging method, such as magnetic resonance imaging, makes it difficult to confirm conclusions from our results.[44]

Conclusions

Patients with schizophrenia exhibit thinner RNFL thickness. The decreased thickness of the RNFL may be related to impairment of cognitive tasks requiring visual participation. Cognitive impairment in tasks requiring visual involvement may be closely related to the cell loss of retinal nerve fibers. RNFL degeneration might be a potential biomarker of schizophrenia. The abnormal level of VEGF that might be involved in this degeneration of RNFL through the vascular neuroimmunology process.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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