



Non-linear associations between retinal nerve fibre layer (RNFL) and positive and negative symptoms among men with acute and chronic schizophrenia spectrum disorder

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ABSTRACT

Background: Schizophrenia Spectrum Disorder (SSD) is a chronic psychiatric disorder with modest treatment outcomes. Changes in neuronal morphology may be associated with the symptomatology of SSD. In the present study, we compared the retinal nerve fibre layer thickness (RNFLT) of typically developed adults with that of individuals with SSD in both acute and chronic stages.

Methods: Fifteen healthy adult males (mean age: 36.40 years) and 30 individuals with SSD (mean age: 37.9 years) took part in the study. Among the latter, 15 had a chronic mean SSD for 15.33 years, while 15 were in an acute psychotic phase with a mean illness duration of 12.20 years. Experts rated positive and negative symptoms of SSD. Retinal nerve fibre layer thickness (RNFLT) of all participants was measured with optical coherence tomography (OCT).

Results: Compared to healthy controls, individuals with acute SSD had the lowest macula thickness in the right eye. For nerve fiber layer atrophy, participants with acute SSD showed the largest atrophy (right eye, inferior quadrant). For retinal thickness and macular volume cube, compared to healthy controls, participants with acute SSD had the lowest thickness in the subfield of the right eye. Non-linear associations were observed between RNFL and positive and negative symptoms: e.g., for macula central and subfoveal thickness (left and right eye) and for participants with both acute and chronic SSD, exclusively positive and exclusively negative symptoms (as opposed to prevalently negative with some positive symptoms or prevalently positive with some negative symptoms) were associated with lower volumes. In participants with acute SSD, a longer disease duration was associated with thicker RNFL, while in participants with a chronic SSD a longer disease duration was associated with a thinner RNFL.

Conclusion: The present results confirm previous findings that specific neuronal morphological abnormalities can be observed among individuals with SSD. The non-linear associations between neuronal alterations and positive and negative symptomatology suggested that higher pronounced SSD severity appears to be particularly related to morphological changes. Disease duration and RNFL thickness were linearly associated, though, in opposite directions depending on the chronic or acute state.

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1. Introduction

Schizophrenia spectrum disorder (SSD) covers a broad range of symptoms observable at different time points. Typically, individuals with SSD display disorganization in formal thoughts and language, hallucinations, delusions, catatonic symptoms, dysfunctions in affect and mood, self-disorder, somatic symptoms, and neurocognitive impairments (Falkai et al., 2015; Leucht et al., 2019). Up to 50% of individuals with SSD show functional impairments, an elevated risk of permanent unemployment, and a relative inability to build and maintain stable relationships. Treatment outcomes are modest, and comorbidities such as heavy tobacco use, obesity, diabetes are often observed (Falkai et al., 2015; Kahn et al., 2015; Leucht et al., 2019).

Results from imaging studies (Farnia et al., 2019; Shenton et al., 2001; van Erp et al., 2018; Vitolo et al., 2017) indicate that, compared to typically developing adults, individuals with SSD display specific morphological and functional brain alterations. For example, individuals with SSD show reduced brain volumes in the fronto-temporo-thalamic regions (Fornito et al., 2009), specific disruptions of both grey (Olabi et al., 2011) and white matter areas such as long projection fibres, callosal and commissural fibres, part of the motor-descending fibres, and fronto-temporal-limbic pathways (Vitolo et al., 2017). In addition, adults with SSD have a thinner cortex, a smaller surface area, particularly in both frontal and temporal lobe regions (van Erp et al., 2018). Lower regional cortical thickness has been associated with higher normalized medication dose, higher symptom severity, and longer duration of illness, and with an earlier age of onset (van Erp et al., 2018).

Methods derived from ophthalmology have opened a completely new avenue of research into brain tissue in vivo. Thus, optical coherence tomography (OCT) is a high-resolution reproducible imaging technology allowing measurement of structural peculiarities of the retinal nerve fibre layers (RNFL), retinal nerve fibre layer thickness (RNFLT), macular volume (MV) and macular thickness (MT); these are considered the “window of the brain”. The RNFL is principally composed of ganglion cell axons, which form the optic nerve, chiasm, and optic tracts (Galetta et al., 2011; Savini et al., 2005; Zaveri et al., 2008). The uniqueness of the RNFL lies in its lack of a myelin layer. No other central nervous system tract has this unique arrangement, which provides a visual pathway to investigate the extension of the brain, given that from an embryological perspective nerve fibres and brain tissue are identical. Thus, following Schönfeldt-Lecuona et al. (2016) the unmyelinated RNFL is a unique anatomical model because it enables insight into the pathophysiological processes of diseases such as neurodegenerative diseases. Relatedly, Schönfeldt-Lecuona et al. (2016) also noted that impairments in visual function are often observed in neurodegenerative disorders such as Alzheimer’s Disease and Parkinson’s disease, and also in inflammatory diseases such as Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder. Schönfeldt-Lecuona et al. (2016) concluded that OCT allows precise detection and evaluation of different single retinal layers (that is, the retinal architecture also including macular volume and macular thickness) and subtle changes in these.

Optical Coherence Tomography (OCT) has already been employed to measure RNFL(T) in individuals with SSD. In order of publication, the following findings have been reported. Ascaso et al. (2010) compared RNFLT via OCT in 10 individuals with and 10 individuals without SSD and observed that compared to the healthy controls, individuals with SSD had a significant reduction in both overall and nasal RNFLT. Chu et al. (2012) compared RNFLT of 49 SSD individuals with those of 40 healthy controls, but found no significant differences. Lee et al. (2013) compared RNFLT traits of 30 individuals with and 30 individuals without SSD. Compared to controls, individuals with SSD had thinner peripapillary RNFLT in superior, inferior, and temporal quadrants, but not in nasal quadrants, along with lower macula thickness (MT) and macula volume (MV). Importantly, for those individuals with SSD, a longer illness duration (acute phase: < 2 years; chronic illness: between

two and 10 years; very long illness: > 10 years) was associated with thinner RNFLT and MT, and lower MV. Ascaso et al. (2015) compared RNFLT dimensions of 30 controls and 30 individuals with SSD; of these latter, 10 had a recent illness episode, and 20 had a chronic illness episode. Compared to healthy controls, individuals with SSD had thinner RNFLT (overall; nasal; superior; inferior quadrant), a thinner MT and lower MV. More specifically, individuals in a chronic illness episode, but not those in an acute/psychotic phase of SSD, had significantly lower RNFLT, MT and MV measurements. A further exploratory analysis revealed that illness duration was *unrelated* to RNFLT, MT or MV, when controlling for age, suggesting that biological age, but not illness duration per se, was the determining factor. This finding could be understood as reflecting a neuronal progression of degeneration as a function of age rather than as a function of disease duration. Interestingly, while negative and positive symptoms of SSD were assessed, they were not compared to values for the RNFLT, MT and MV dimensions. Schönfeldt-Lecuona et al. (2019) compared RNFLT, MT and MV of 26 individuals with and 23 without SSD. Compared to controls, individuals with SSD had reduced thickness and volume measures on nearly all RNFLT, and MT and MV measures. In addition, longer disease duration was associated with a thinner total volume of RNFLT. In their systematic review and meta-analysis Kazokas and Karageorgiou (2020) concluded that associations between thinner RNFLT and SSD could be confirmed, but that methodological issues such as diagnostic accuracy and the small sample sizes might blur the overall pattern. Likewise, Silverstein et al. (2019) concluded from their review that, compared to healthy controls, individuals with SSD show both functional and structural abnormalities of brain tissue, while possible confounders such as small sample sizes, anti-psychotic medication, smoking, obesity and diabetes might have prevented a clearer picture from emerging. These authors also queried whether and if so to what extent the present status of brain tissue reflects a state or a trait. To put it the other way around, do impairments in RNFL reflect a process of neurodegeneration or neuro-impairment, or abnormal generation (Kahn et al., 2015), or even more simply a state of failed neuro-regeneration (Falkai et al., 2015)?

To summarize, there is evidence to indicate that, compared to healthy controls, individuals with SSD have impairments in RNFLT as assessed via OCT. On the other hand, it remains unclear whether alterations in RNFLT reflect dysfunctional illness-related (i.e., illness duration) alterations as an ongoing neurochemical and morphologic process. Surprisingly, to our knowledge previous studies have not systematically related the current status of symptoms (here: positive and negative symptoms) with RNFLT (for an exception, see Ascaso et al., 2015).

Given this background, two hypotheses and one research question were formulated. First, following others (Ascaso et al., 2010; Ascaso et al., 2015; Schönfeldt-Lecuona et al., 2019; Schönfeldt-Lecuona et al., 2016), we anticipated that, compared to healthy controls, individuals with SSD would have thinner RNFLT, including macular volume and macular thickness. Second, following Lee et al. (2013) and Schönfeldt-Lecuona et al. (2019) we expected that RNFLT, macular volume and macular thickness would be negatively related to disease duration. The research question was whether and if so to what extent dimensions of RNFL are associated with current positive and negative symptoms of SSD. To test the hypotheses and address the research question, we assessed RNFLT, MT and MV, and the current state of positive and negative SSD symptoms in 15 individuals with chronic SSD, in 15 individuals in an acute state of SSD, and in 15 healthy controls.

2. Method

2.1. Procedure

Individuals with SSD resident in the Psychiatric Ward of the Sina Hospital of the Hamadan University of Medical Sciences (Hamadan, Iran) were approached to participate in the study. In parallel, healthy age- and gender-matched controls were recruited. All participants were

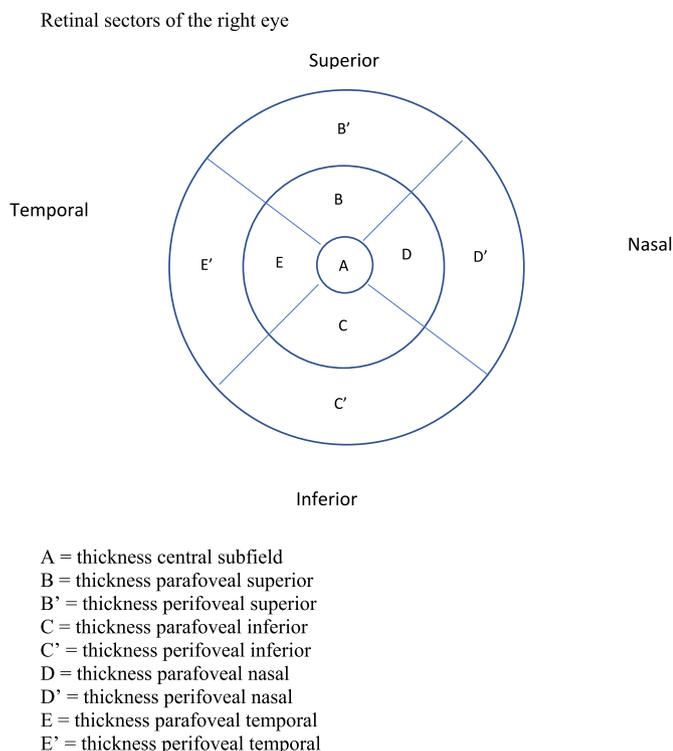


Fig. 1. Retinal sectors of the right eye.

informed about the study aims and the confidential and anonymous data handling. Thereafter, participants gave their signed written informed consent. After a thorough psychiatric interview (including assessment of positive and negative symptoms) and ophthalmologic assessment, all participants underwent OCT (see below). The study was executed between January 2019 and November 2019. The local ethics committee of the University of Hamadan (Hamadan, Iran: code: IR.UMSHA.REC.1397.072) approved the study, which was performed according to the seventh revision (World Medical Association, 2013) of the Declaration of Helsinki.

2.2. Participants

Inclusion criteria were: 1. Male sex; 2. Age between 18 and 65 years; 3. Diagnosis of SSD, based on the DSM-5 (American Psychiatric Association, 2013); 4. Willing and able to comply with the study conditions; 5. Signed written informed consent. 6. Stable antipsychotic medication at therapeutic dosages such as clozapine, olanzapine, quetiapine, aripiprazole, risperidone, or paliperidone. 7. BMI between 18 and 28. 8. High quality images (signal strengths higher than 6/10 points). Exclusion criteria were: 1. Other severe psychiatric issues such as substance abuse, as determined during the clinical interview and based on medical records. Substances included opium, opioids, cannabis, alcohol, amphetamine, methamphetamine, and other hallucinogens. Heavy tobacco use was not an exclusion criterion. 2. Severe ophthalmological issues such as glaucoma, age-related macular degeneration, media opacity with poor quality index in OCT printout and high refractive error >4 spherical diopters; relatedly, we considered all ophthalmic pathologies with BCVA lesser than 5/10 as severe, along with all cases with ocular pathologies that could potentially affect nerve fiber layer and macular thickness measurement. 3. Severe metabolic and endocrinological issues such as diabetes, particularly high or low cortisol, cholestenone, or insulin concentrations, as ascertained by a thorough lab analysis. More specifically, the following cut-off values were used: fasting blood sugar >140 mg/dL; cortisol level: range between 6 and 23 µg per deciliter (mcg/dL); cholesterol >200 mg/dL; 4. The investigator had the option of excluding

a participant displaying low compliance across the testing period, and when a participant had issues with regular medication intake, mentioned suicidal ideations, or when general health worsened unexpectedly.

Of the 35 individuals in an acute phase of SSD, 15 (42.8%) agreed to or were eligible for participation. Of the 40 in a chronic state of SSD, 15 (37.5%) agreed to or were eligible for participation. The main reasons for exclusion or non-eligibility were: suicidal ideations; worsening symptoms of SSD; no interest in participation; non-adherence to the overall treatment regimen.

2.3. Sample of healthy controls

Healthy controls were recruited via advertisements among university and clinical staff members. Inclusion criteria were: 1. Male gender; 2. Age between 18 and 65 years; 3. Physically and psychopathologically healthy, as ascertained by a thorough medical check and psychiatric interview led by experienced clinical psychologists; 4. Willing and able to comply with the study conditions; 5. Signed written informed consent. 6. BMI between 18 and 28. 7. High-quality images (signal strengths higher than 6/10 points). Exclusion criteria were: 1. Severe psychiatric issues such as substance abuse (opium, opioids, cannabis, alcohol, amphetamine, methamphetamine, and other hallucinogens; again, heavy tobacco use was not an exclusion criterion); to this end, a clinical psychologist or psychiatrist not involved in the study performed a thorough clinical interview for psychiatric disorders based on the DSM-5 (First, 2015). 2. Severe ophthalmological issues such as glaucoma, age-related macular degeneration, media opacity with poor quality index in OCT printout and high refractive error >4 spherical diopters. Relatedly, as for individuals with SSD, we treated all ophthalmic pathologies with BCVA lesser than 5/10 as severe, along with all cases with ocular pathologies that could potentially affect nerve fiber layer and macular thickness measurement. 3. Severe metabolic and endocrinological issues such as diabetes, particularly high or low cortisol, cholestenone, or insulin concentrations, as ascertained by a thorough lab analysis. The same cut off values were applied as for individuals with SSD. 4. The investigator had the option of excluding a participant with low compliance over the course of the testing period. Of the 18 eligible participants approached, 15 (83.4%) were included in the study; three withdrew from the study due to time and work constraints.

2.4. Tools

2.4.1. Sociodemographic and illness-related information

Age was provided by participants. For individuals with SSD, illness-related information including current medication, tobacco use, and illness duration were taken from their medical records.

2.4.2. Illness severity; positive and negative syndromes

The Farsi version (Ghamari-Givi, 2010) of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was employed to assess illness severity. The PANSS is a clinical interview which takes about 30–45 min. Dimensions of the positive syndrome are for instance delusions, hallucinations, and self-disorder, while dimensions of the negative syndrome include disorganization in formal thoughts and language, catatonic symptoms, social withdrawal and dysfunctions in affect and mood. The current status refers to the last seven days. Illness severity is assessed on a seven-point rating scale ranging from 1 (= not observable) to 7 (= extremely observable). For example: "hallucinations: 4 = medium severity: hallucinations occur often but not permanently; thoughts and behavior are only marginally impaired". Higher sum scores reflect a more pronounced symptomatology. Based on the sum scores, participants were labeled as follows: only positive symptoms; prevalently positive and some negative symptoms; prevalently negative and some positive symptoms; only negative symptoms.

Table 1

Descriptive and inferential statistical indices of Retinal Nerve Fiber Layer Thickness (RNFT) and macular volume and thickness, separately for healthy controls (N = 15), individuals with acute schizophrenia spectrum disorder (SSD; N = 15) and with chronic schizophrenia spectrum disorder (SSD; n = 15).

| | Groups | | | Statistics | |
|--|----------------------------------|---------------------------|-----------------------------|-----------------------|--|
| | Healthy controls 15 M (SD) | Acute SSD 15 M (SD) | Chronic SSD 15 M (SD) | F (2, 42), η_p^2 | Significant post-hoc group comparisons |
| Macular thickness; central and subfoveal | | | | | |
| Right eye | 260.47 (21.74) | 235.87 (17.73) | 240.00 (37.72) | 3.53* .144 (L) | Acute SSD < HC |
| Left eye | 262.07 (23.50) | 241.53 (29.17) | 243.73 (26.33) | 2.73 .115 (M) | – |
| Macular volume (mm3) | | | | | |
| Right eye | 10.18 (0.48) | 9.89 (0.59) | 9.87 (0.62) | 1.42 .063 (M) | – |
| Left eye | 10.17 (.047) | 10.05 (0.54) | 10.00 (0.58) | 0.43 .020 (S) | – |

Notes: HC = healthy controls; SSD = schizophrenia spectrum disorder; * = p < .05; S = small effect size; M = medium effect size; (L) = large effect size, post-hoc comparisons: = = equal to; > = larger than; < = smaller than.

Table 2

Descriptive and inferential statistical indices of macular thickness (distance between the retinal internal limiting membrane and retinal pigment epithelium, separately for healthy controls (N = 15), individuals with chronic schizophrenia spectrum disorder (SSD; N = 15) and with acute schizophrenia spectrum disorder (SSD; n = 15).

| | Groups | | | Statistics | |
|-------------------------------|----------------------------------|---------------------------|-----------------------------|-----------------------|--|
| | Healthy controls 15 M (SD) | Acute SSD 15 M (SD) | Chronic SSD 15 M (SD) | F (2, 42), η_p^2 | Significant post-hoc group comparisons |
| Parafoveal Superior right eye | 282.00 (8.27) | 282.33 (23.04) | 271.66 (19.62) | 1.68 .074 (M) | – |
| Superior left eye | 286.33 (14.20) | 284.87 (25.89) | 278.40 (19.47) | 0.64 .030 (S) | – |
| Perifoveal Superior right | 331.07 (15.89) | 320.00 (24.42) | 327.53 (27.99) | 0.88 .040 (S) | – |
| Superior left | 329.13 (15.75) | 327.73 (17.73) | 330.47 (31.59) | 0.05 .003 (T) | – |
| Parafoveal inferior right | 272.67 (12.65) | 268.13 (18.60) | 270.27 (19.90) | 0.25 .012 (T) | – |
| inferior left | 274.53 (10.06) | 267.33 (18.25) | 268.87 (16.80) | 0.90 .041 (S) | – |
| Perifoveal inferior right | 327.60 (13.26) | 315.40 (22.85) | 316.00 (26.56) | 1.52 .067 (M) | – |
| inferior left | 329.60 (13.49) | 325.60 (21.71) | 314.60 (24.80) | 2.14 .092 (M) | – |
| Parafoveal temporal right | 267.27 (10.05) | 261.60 (13.65) | 261.00 (15.88) | 0.99 .045 (S) | – |
| temporal left | 265.60 (16.85) | 266.87 (13.16) | 261.47 (17.60) | 0.47 .022 (S) | – |
| Perifoveal temporal right | 319.27 (15.78) | 310.13 (12.58) | 308.13 (22.16) | 1.76 .078 (M) | – |
| temporal left | 317.27 (15.76) | 316.607 (28.33) | 309.73 (24.80) | 0.47 .022 (S) | – |
| Parafoveal nasal right | 309.33 (27.05) | 297.40 (18.23) | 292.20 (23.48) | 1.13 .051 (S) | – |
| nasal left | 302.40 (13.09) | 305.73 (28.50) | 298.33 (23.20) | 0.40 .019 (T) | – |
| Perifoveal nasal right | 324.60 (30.95) | 321.20 (16.53) | 330.93 (28.20) | 0.54 .025 (S) | – |
| nasal left | 332.53 (15.42) | 325.53 (16.53) | 327.67 (20.07) | 0.49 .023 (S) | – |

Notes: HC = healthy controls; SSD = schizophrenia spectrum disorder; * = p < .05; S = small effect size; M = medium effect size; (L) = large effect size, post-hoc comparisons: = = equal to; > = larger than; < = smaller than.

Table 3

Descriptive and inferential statistical indices of retinal nerve fiber layer atrophy in the superior, inferior, nasal, and temporal quadrants of right and left eye, separately for healthy controls (N = 15), individuals with acute schizophrenia spectrum disorder (SSD; N = 15) and with chronic schizophrenia spectrum disorder (SSD; n = 15).

| | Groups | | | Statistics | |
|-------------------------|----------------------------------|---------------------------|-----------------------------|-----------------------|--|
| | Healthy controls 15 M (SD) | Acute SSD 15 M (SD) | Chronic SSD 15 M (SD) | F (2, 42), η_p^2 | Significant post-hoc group comparisons |
| Superior right | 0.27 (0.70) | 0.40 (0.83) | 0.33 (0.90) | 0.10 .005 (T) | – |
| Superior left | 0.20 (0.56) | 0.53 (1.12) | 0.13 (0.52) | 1.12 .051 (S) | – |
| inferior right | 0.00 (0.00) | 0.80 (1.21) | 0.53 (0.99) | 3.06 .127 (M) | – |
| inferior left | 0.00 (0.00) | 0.53 (1.12) | 1.20 (1.42) | 4.94* .19 (L) | HC < Chronic SSD |
| temporal right | 0.67 (0.26) | 0.53 (1.12) | 0.33 (0.90) | 1.15 .052 (S) | – |
| temporal left | 0.20 (0.77) | 0.00 (0.00) | 1.00 (1.30) | 5.44* .21 (L) | Acute SSD < Chronic SSD |
| nasal right | 0.20 (0.56) | 0.27 (0.70) | 0.60 (1.24) | 0.88 .04 (T) | – |
| nasal left | 0.20 (0.56) | 0.13 (0.52) | 0.47 (1.06) | 0.82 .038 (S) | – |
| Average thickness right | 91.06 (8.95) | 84.67 (13.64) | 85.40 (11.31) | 1.40 .063 (M) | – |
| Average thickness left | 92.47 (9.32) | 91.73 (10.21) | 85.13 (15.81) | 1.66 .073 (M) | – |
| Symmetry | 72.93 (23.79) | 73.67 (19.30) | 75.67 (20.04) | 0.17 .0003 (T) | – |

Notes: HC = healthy controls; SSD = schizophrenia spectrum disorder; * = p < .05; S = small effect size; M = medium effect size; (L) = large effect size, post-hoc comparisons: = = equal to; > = larger than; < = smaller than.

2.4.3. Optical coherence tomography (OCT)

A trained and experienced ophthalmologist was responsible for the assessment of OCT, using a spectral-domain OCT (SD-OCT) system (Cirrus HD-OCT 5000; Carl Zeiss Medical Technology AG, Jena, Germany) and following dilation of the pupils with 0.5% tropicamide. As mentioned above, only high-quality images (signal strengths higher than 6/10 points) were included for further analysis. Scans of peripapillary RNFL thickness, macular thickness and macular volume were performed for both eyes. Macular thickness was measured in the central region and upper-inferior-nasal-temporal quadrants. We followed Schuman et al. (1996) and Ascano et al. (2015) and acquired RNFL by tacking three circumpapillary scans of 3.4 mm diameter centered on the optic disc in

Table 4

Descriptive and inferential statistical indices of retinal thickness and volume cube, separately for healthy controls (N = 15), individuals with acute schizophrenia spectrum disorder (SSD; N = 15) and with chronic schizophrenia spectrum disorder (SSD; n = 15).

| | Groups | | | Statistics | |
|---------------------------------------|-------------------|-------------------|-------------------|--------------------------|--|
| | Healthy controls | Acute SSD | Chronic SSD | | Significant post-hoc group comparisons |
| N | 15 | 15 | 15 | F (2, 42), η_p^2 | |
| | M (SD) | M (SD) | M (SD) | | |
| Macular thickness central (subfoveal) | | | | | |
| Right eye | 260.47 (21.73) | 235.87 (17.73) | 240.00 (37.72) | 3.53* .144 (L) | Acute SSD < HC |
| Left eye | 262.07 (23.50) | 241.53 (29.17) | 243.73 (26.32) | 2.73 .115 (M) | – |
| Volume cube (mm ³) | | | | | |
| Right eye | 10.18 (0.48) | 9.89 (0.59) | 9.87 (0.62) | 1.42 .068 (M) | – |
| Left eye | 10.17 (0.47) | 10.05 (0.54) | 10.00 (0.58) | 0.43 .020 (S) | – |
| Thickness average cube (micron) | | | | | |
| Right eye | 275.67 (30.03) | 275.67 (15.93) | 275.00 (16.26) | 0.004 .000 (T) | – |
| Left eye | 282.60 (13.42) | 278.87 (14.53) | 277.67 (16.19) | 0.46 .021 (S) | – |

Notes: HC = healthy controls; SSD = schizophrenia spectrum disorder; * = p < .05; S = small effect size; M = medium effect size; (L) = large effect size, post-hoc comparisons: = = equal to; > = larger than; < = smaller than.

order to intercept all nerve fibers converging toward the optic disc. Outcome dimensions were the average of the three scans.

The following indices were assessed:

Optic nerve head (optic disc): 1. Average retinal nerve fiber layer thickness (mm³); 2. Retinal nerve fiber layer symmetry between right and left eye; 3. Neuroretinal rim area (mm³); 4. Optic disc area (mm³); 5. Average cup to disc ratio; 6. Vertical cup to disc ratio; 7. Cup volume (mm³).

Retinal (macular) thickness: 1. Retinal thickness in the macular region of the central (subfoveal) area; 2. Retinal thickness of the parafoveal area in four quadrants: superior, inferior, nasal, temporal and in the perifoveal area, again in four quadrants.

In all quadrants thickness was calculated from ILM (internal limiting membrane) to RPE (retinal pigment epithelium layer) of the retina. Macular volume and average thickness of macula was also measured by means of OCT.

Fig. 1: A schematic graph of CIRRUS 5000 OCT shows the parameters mentioned in the text.

2.5. Statistical analysis

The sociodemographic characteristics of the three groups were compared by Chisquare tests and ANOVAs.

Multivariate ANOVAs were computed for the dimensions of the macula and retinal nerve fiber layer thickness of the three groups. Where appropriate, post-hoc analyses were performed employing Bonferroni-Holm corrections for p-values. Effect size calculations were reported as partial eta-squared (η_p^2) with the following cut-offs: 0.01 ≤ η_p^2 < 0.019: trivial effect size; 0.020 ≤ 0.059: small effect size; 0.06 ≤ η_p^2 < 0.139: medium effect size; 0.14 > η_p^2 : large effect size.

Two t-tests were calculated for the differences in symptom severity

Table 5

Descriptive and inferential statistical indices of optic nerve head parameters including neuroretinal Rim and disc area, cup-to-disk ratio and cup volume separately for individuals with acute schizophrenia spectrum disorder (SSD; N = 15) and with chronic schizophrenia spectrum disorder (SSD; n = 15).

| | Groups | | Statistics | |
|-------------------------------------|-----------------|-----------------|--------------------------|--|
| | Acute SSD | Chronic SSD | | Significant post-hoc group comparisons |
| N | 15 | 15 | F (1, 28), η_p^2 | |
| | M (SD) | M (SD) | | |
| Rim area right eye | 1.44 (0.17) | 1.50 (0.42) | 0.27 .01 (T) | – |
| Rim area left eye | 1.34 (0.24) | 1.56 (0.50) | 2.46 .081 (M) | – |
| Disk area right eye | 1.85 (0.32) | 1.88 (0.44) | 0.03 .001 (T) | – |
| Disk area left | 1.76 (.38) | 1.96 (0.53) | 1.49 .05 (S) | – |
| Average cup-to-disk ratio right eye | 0.43 (0.18) | 0.40 (0.19) | 0.16 .006 (T) | – |
| Average cup-to-disk ratio left eye | 0.42 (0.17) | 0.41 (0.17) | 0.01 .000 (T) | – |
| Vertical cup-to-disk right eye | 0.39 (0.17) | 0.34 (0.21) | 0.52 .018 (T) | – |
| Vertical cup-to-disk left eye | 0.41 (0.16) | 0.34 (0.18) | 0.07 .003 (T) | – |
| Cup volume right eye | 0.12 (0.10) | 0.10 (0.12) | 0.01 .000 (T) | – |
| Cup volume left eye | 0.10 (0.93) | 0.10 (0.16) | 0.005 .000 (T) | – |
| Symptom severity | 2.67 (1.17) | 2.93 (1.16) | 0.39 .014 (T) | – |
| Symptom duration | 12.20 (5.48) | 13.77 (7.87) | 1.20 .041 (S) | – |

Notes: Rim = Neuroretinal rim (the tissue between the border of the cup and the disc); SSD = schizophrenia spectrum disorder; * = p < .05; S = small effect size; M = medium effect size; (L) = large effect size, post-hoc comparisons: = = equal to; > = larger than; < = smaller than.

and symptom duration between individuals with SSD during an acute or chronic state.

Pearson’s linear and non-linear correlations were computed between symptom severity and symptom duration and dimension of RNFL, separately for individuals with SSD in an acute or chronic state.

The level of significance was set at alpha < .05. All computations were performed with SPSS® 25.0 (IBM Corporation; Armonk NY, USA) for Apple Mac®.

3. Results

3.1. Participants

There were no differences in age between individuals with SSD in an acute stage (M = 37.66 years; SD = 9.24), chronic stage (M = 38.26 years; SD = 7.90) or healthy control (M = 36.40 years; SD = 9.51). Disease duration was 12.30 (8.48) years for individuals in an acute state, and 15.33 (9.65) years for individuals with SSD in a chronic state (t (28) = 1.09, p = .28, d = 0.39).

3.2. Retinal nerve fiber layer thickness, macular volume and thickness

Tables 1–5 report all descriptive and inferential statistical indices for the dimensions of RNFL and macula between individuals with acute and chronic SSD and healthy controls. If not otherwise reported, no descriptive or statistically significant mean differences were observed between the three groups. In addition, all statistical indices are reported in the Tables and not repeated in the text.

Table 6

Correlations between disease duration and indices of retinal nerve fiber layer and macula, separately for individuals with acute and chronic schizophrenia spectrum disorder.

| | Group | |
|--|-----------|-------------|
| | Acute SSD | Chronic SSD |
| N | 15 | 15 |
| Macula thickness central and subfoveal right | 0.47 | -0.40 |
| Macula thickness central and subfoveal left | 0.07 | -0.15 |
| Optic nerve volume right | 0.33 | -0.55 |
| Optic nerve volume left | 0.24 | -0.49 |
| Macula thickness average cup right | 0.33 | -0.58 |
| Macula thickness average cup left | 0.25 | -0.50 |
| Internal limiting membrane to retinal pigment epithelium parafoveal superior right | -0.07 | -0.50 |
| Internal limiting membrane to retinal pigment epithelium prefoveal superior right | 0.16 | -0.07 |
| Internal limiting membrane to retinal pigment epithelium parafoveal inferior right | 0.34 | -0.59 |
| Internal limiting membrane to retinal pigment epithelium prefoveal inferior right | 0.29 | -0.27 |
| Internal limiting membrane to retinal pigment epithelium parafoveal temporal right | 0.35 | -0.38 |
| Internal limiting membrane to retinal pigment epithelium prefoveal temporal right | -0.09 | -0.49 |
| Internal limiting membrane to retinal pigment epithelium parafoveal nasal right | 0.29 | -0.62 |
| Internal limiting membrane to retinal pigment epithelium prefoveal nasal right | -0.03 | -0.07 |
| Internal limiting membrane to retinal pigment epithelium parafoveal superior left | -0.01 | -0.43 |
| Internal limiting membrane to retinal pigment epithelium prefoveal superior left | 0.09 | -0.53 |
| Internal limiting membrane to retinal pigment epithelium parafoveal inferior left | 0.46 | -0.60 |
| Internal limiting membrane to retinal pigment epithelium prefoveal inferior left | 0.44 | -0.50 |
| Internal limiting membrane to retinal pigment epithelium parafoveal temporal left | 0.26 | -0.44 |
| Internal limiting membrane to retinal pigment epithelium prefoveal temporal left | 0.18 | -0.41 |
| Internal limiting membrane to retinal pigment epithelium parafoveal nasal left | 0.01 | -0.64 |
| Internal limiting membrane to retinal pigment epithelium prefoveal nasal left | -0.11 | -0.52 |
| Retinal nerve fiber layer superior change atrophy right | -0.43 | -0.14 |
| Retinal nerve fiber layer inferior change atrophy right | -0.40 | 0.11 |
| Retinal nerve fiber layer nasal change atrophy right | -0.53 | -0.04 |
| Retinal nerve fiber layer temporal change atrophy right | -0.35 | 0.03 |
| Retinal nerve fiber layer superior change atrophy left | -0.57 | 0.13 |
| Retinal nerve fiber layer inferior change atrophy left | -0.35 | 0.20 |
| Retinal nerve fiber layer nasal change atrophy left | -0.21 | -0.12 |
| Retinal nerve fiber layer temporal change atrophy left | | 0.62 |
| Retinal nerve fiber layer thickness average right | 0.55 | -0.60 |
| Retinal nerve fiber layer thickness average left | 0.38 | -0.42 |
| Retinal nerve fiber layer symmetry | 0.29 | -0.21 |
| RIM-area-right | 0.40 | -0.002 |
| Disc-area-right | 0.47 | 0.18 |
| Cup-to-disk ratio right | 0.17 | 0.24 |
| Cup-to-disk ratio vertical right | 0.25 | 0.39 |
| Cup-volume right | 0.24 | 0.21 |
| RIM-area-left | 0.59 | -0.09 |
| Disc-area-left | 0.54 | -0.06 |
| Cup-to-disk ratio left | 0.07 | 0.02 |
| Cup-to-disk ratio vertical left | 0.03 | -0.03 |
| Cup-volume left | -0.11 | 0.24 |
| Sign-severity | -0.27 | 0.47 |
| Sign-duration | 1.00 | 1.00 |
| Thickness central subfield right eye | 0.47 | -0.40 |
| Thickness central subfield left eye | 0.07 | -0.15 |
| Volume cube right eye | 0.33 | -0.55 |
| Volume cube left eye | 0.24 | -0.49 |
| Internal limiting membrane to retinal pigment epithelium parafoveal right | -0.08 | -0.51 |
| OD.ILM.Rpe prefoveal sup | 0.15 | -0.07 |
| Thickness average cube right | 0.33 | -0.58 |

Table 6 (continued)

| | Group | |
|--|-----------|-------------|
| | Acute SSD | Chronic SSD |
| Thickness average cube left | 0.25 | -0.50 |
| OD.ILM.Rpe prefoveal inf | 0.39 | -0.59 |
| Internal limiting membrane to retinal pigment epithelium parafoveal inferior right | 0.29 | -0.27 |
| Internal limiting membrane to retinal pigment epithelium parafoveal temporal right | 0.35 | -0.38 |
| Internal limiting membrane to retinal pigment epithelium parafoveal temporal right | 0.74 | -0.49 |
| Internal limiting membrane to retinal pigment epithelium parafoveal nasal right | 0.29 | -0.62 |
| Internal limiting membrane to retinal pigment epithelium parafoveal nasal right | -0.03 | -0.07 |
| Internal limiting membrane to retinal pigment epithelium parafoveal superior left | -0.01 | -0.43 |
| Internal limiting membrane to retinal pigment epithelium parafoveal superior left | 0.09 | -0.53 |
| Internal limiting membrane to retinal pigment epithelium parafoveal inferior left | 0.46 | -0.60 |
| Internal limiting membrane to retinal pigment epithelium parafoveal temporal left | 0.18 | -0.40 |
| Internal limiting membrane to retinal pigment epithelium parafoveal temporal left | 0.44 | -0.50 |
| Internal limiting membrane to retinal pigment epithelium parafoveal nasal left | 0.26 | -0.44 |
| Internal limiting membrane to retinal pigment epithelium parafoveal nasal left | 0.01 | -0.64 |
| Internal limiting membrane to retinal pigment epithelium parafoveal nasal left | -0.11 | -0.52 |
| Retinal nerve fiber layer superior change atrophy right | -0.43 | -0.01 |
| Retinal nerve fiber layer inferior change atrophy right | -0.39 | 0.10 |
| Retinal nerve fiber layer nasal change atrophy right | -0.53 | -0.04 |
| Retinal nerve fiber layer temporal change atrophy right | -0.35 | 0.03 |
| Retinal nerve fiber layer superior change atrophy left | -0.57 | 0.13 |
| Retinal nerve fiber layer inferior change atrophy left | -0.35 | 0.20 |
| Retinal nerve fiber layer nasal change atrophy left | -0.21 | -0.12 |
| Retinal nerve fiber layer temporal change atrophy left | | 0.62 |
| Retinal nerve fiber layer thickness average right | 0.55 | -0.60 |
| Retinal nerve fiber layer symmetry | 0.29 | -0.21 |
| RIM-area right | 0.40 | -0.002 |
| Disc-area right | 0.47 | 0.18 |
| Cup-to-disk ratio right | 0.17 | 0.24 |
| Cup-to-disk ratio vertical right | 0.25 | 0.36 |
| Cup-volume right | 0.24 | 0.21 |
| RIM-area left | 0.59 | -0.09 |
| Disc-area left | 0.54 | -0.06 |
| Cup-to-disk ratio left | 0.07 | 0.02 |
| Cup-to-disk ratio vertical left | 0.03 | -0.03 |
| Cup volume left | 0.70 | 0.24 |

Note: SSD = schizophrenia spectrum disorder.

Compared to healthy controls, individuals with acute SSD had the lowest thickness in the subfoveal (central) area on the left eye. No other descriptively or statistically significant mean differences were found for the left eye or for macular volume (left and right eye; see Table 1).

No descriptively or statistically significant mean differences were found for the retinal thickness in the different parafoveal and perifoveal quadrants (see Table 2).

For nerve fiber layer atrophy, participants with acute SSD showed the largest atrophy (right inferior) in the right eye. Participants with chronic SSD had the largest atrophy in the inferior and temporal left area in the left eye (see Table 3).

For retinal thickness and volume cube, compared to healthy controls, participants with acute SSD had the lowest subfoveal thickness in the right eye (see Table 4).

For neuroretinal rim and disc area, cup volume and cup-to-disk ratio, there were no descriptively or statistically significant mean differences (see Table 5)

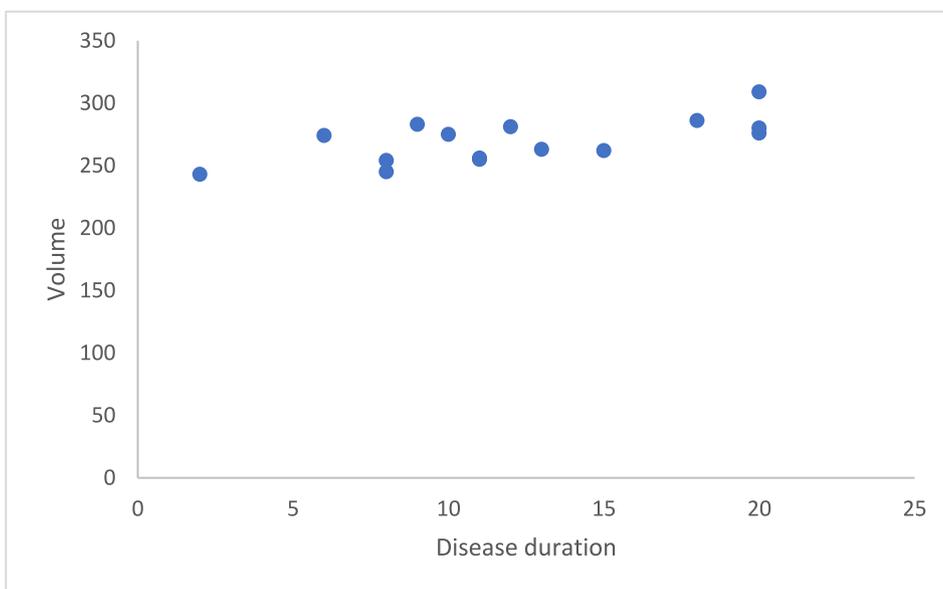


Fig. 2. In participants with acute SSD, greater macular thickness (parafoveal, inferior, left eye) was associated with a longer disease duration: $r = 0.46$.

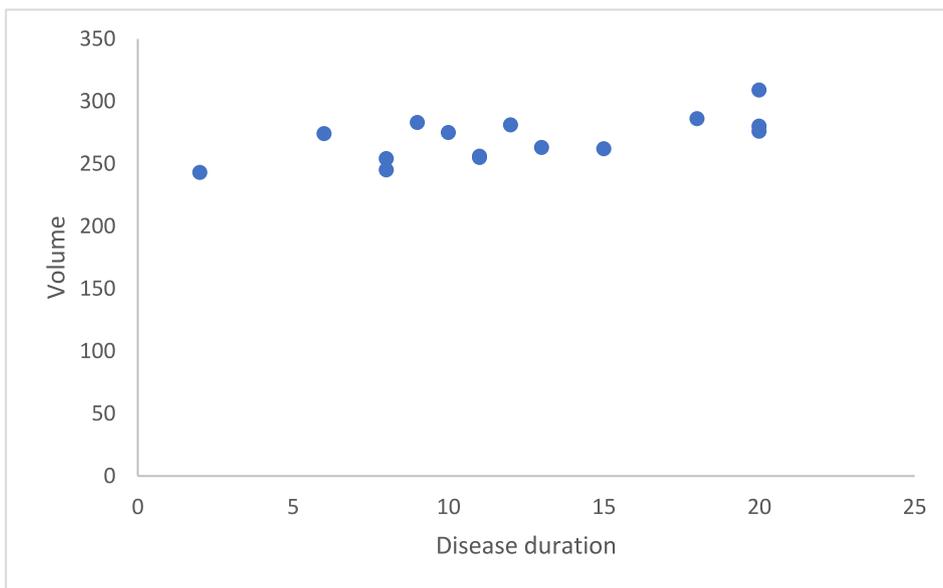


Fig. 3. In participants with acute SSD, greater macular thickness (parafoveal, nasal, right eye) was associated with a longer disease duration: $r = 0.29$.

3.3. Retinal nerve fiber layer thickness, macular volume and thickness and disease duration

Table 6 provides the correlation coefficients between nerve fiber layer thickness, macula volume and thickness and disease duration, separately for individuals with acute and chronic SSD.

For participants with acute SSD, larger dimensions of RNFL were either unrelated or positively associated with a longer disease duration. For example, a greater macular thickness (parafoveal, inferior, left eye (Fig. 2; parafoveal, nasal, right eye, Fig. 3); was associated with a longer disease duration.

For participants with chronic SSD, larger dimensions of RNFL were either unrelated or negatively associated with a longer disease duration. For example, a greater macular thickness (parafoveal, inferior, left eye; Fig. 4; parafoveal, nasal, right eye, Fig. 5) was associated with a shorter disease duration.

As shown in Fig. 5, associations were not linear; while a linear

association yielded a correlation of $r = -0.62$, a non-linear (quadratic) association yielded a correlation of $r = -0.70$; a cubic association yielded a correlation of $r = -0.76$.

3.4. Retinal nerve fiber layer thickness, macular volume and thickness and illness severity; positive and negative syndromes; separately for individuals with acute and chronic schizophrenia spectrum disorder

As noted above, disease severity was assessed via the Positive and Negative Syndrome Scale (PANSS). Based on sum scores, participants were classified as follows: only positive symptoms (= 1); prevalently positive and some negative symptoms (= 2); prevalently negative and some positive symptoms (= 3); only negative symptoms (= 4). Given this categorization linear correlations were inappropriate.

Table 7 provides the overview of non-linear correlation coefficients between symptom characteristics and dimensions of retinal nerve fiber layer and macular, separately for individuals with acute and chronic

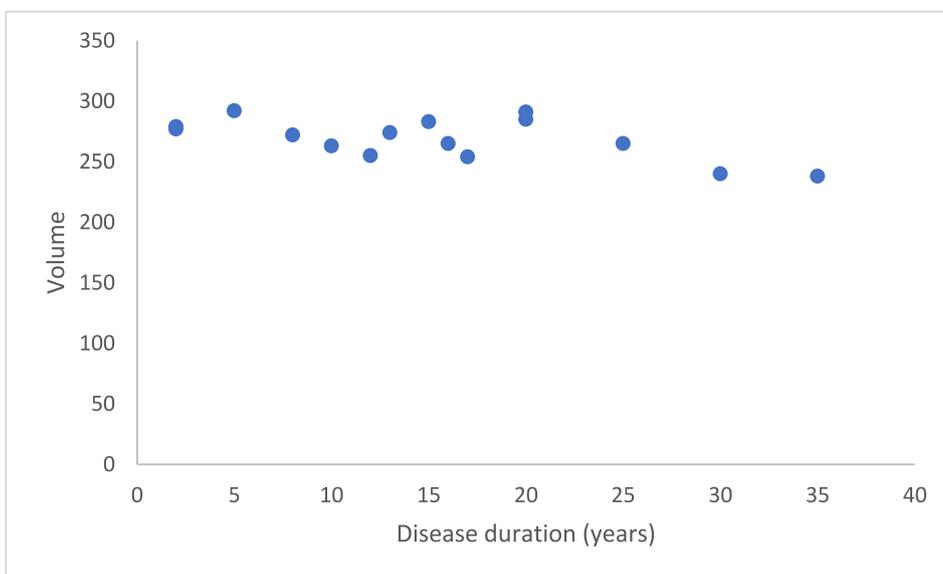


Fig. 4. In participants with chronic SSD, greater macular thickness (parafoveal, inferior, left eye) was associated with a shorter disease duration: $r = -0.60$.

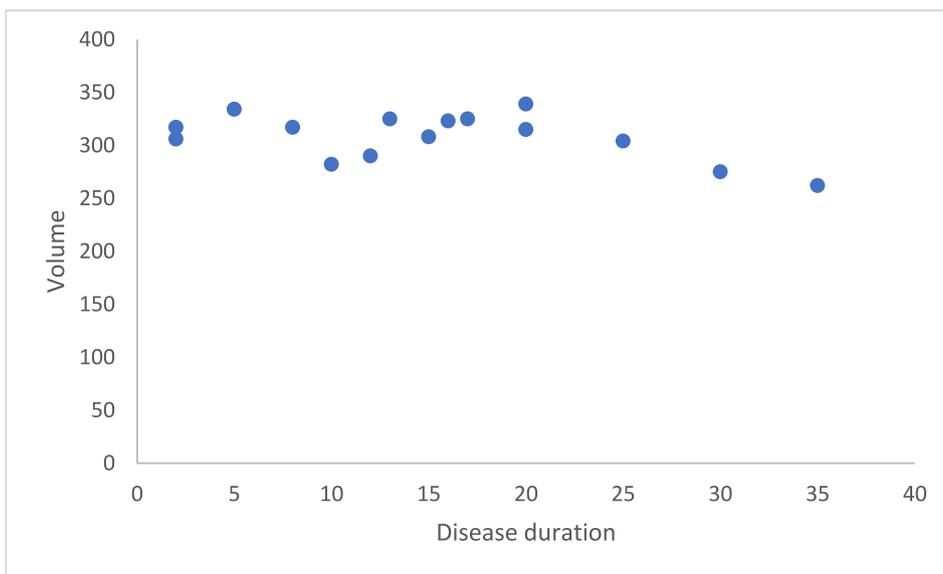


Fig. 5. In participants with chronic SSD, greater macular thickness (parafoveal, nasal, left eye) was associated with a shorter disease duration: $r = -0.62$.

SSD.

For macular central and subfoveal thickness (left and right eye) and for participants with both acute and chronic SSD, only positive and only negative symptoms (as contrasted to prevalently negative with some positive symptoms and to prevalently positive with some negative symptoms) were associated with lower volumes. Fig. 6 shows the non-linear association between the macula thickness (central and subfoveal thickness of the right eye) and symptom characteristics among participants with chronic SSD.

For macular volume (left and right), the pattern was as follows: For participants with chronic SSD only positive and only negative symptoms were associated with lower volumes. For participants with acute SSD volumes decreased in an almost linear fashion from only positive, to prevalently positive, to prevalently negative, to only negative symptoms.

For macular thickness central subfoveal (left and right eye), for participants with chronic SSD only positive and only negative symptoms were associated with lower volumes. For participants with acute SSD,

only positive and only negative symptoms were associated with lower volumes in the left eye, while for the right eye volumes decreased in an almost linear fashion from only positive, to prevalently positive, to prevalently negative, to only negative symptoms.

Fig. 7 shows the non-linear association between the macula thickness subfoveal field of the right eye and symptom categories among individuals with acute SSD.

For macular volume and average thickness of the left and right eye and for participants with acute SSD, volume and thickness decreased in an almost linear fashion from only positive, to prevalently positive, to prevalently negative to only negative symptoms.

For macular volume and average thickness of the left and right eye and for participants with chronic SSD, only positive and only negative symptoms were associated with lower volumes and thickness.

4. Discussion

The key findings of the present study were that, compared to healthy

Table 7

Non-linear correlations between disease severity and indices of retinal nerve fiber layer and macula, separately for individuals with acute and chronic schizophrenia spectrum disorder.

| Group | Acute SSD | | Chronic SSD | |
|--|-----------|---|-------------|---|
| | N | 15 | 15 | - |
| Macula thickness central (subfoveal) right eye | r = .65 | Only positive and only negative symptoms with lower thickness | r = .40 | Only positive and only negative symptoms with lower thickness |
| Macula thickness central (subfoveal) left eye | r = .35 | Only positive and only negative symptoms with lower thickness | r = .25 | Only positive and only negative symptoms with lower thickness |
| Macular volume cube right eye | r = -.565 | Volume decreases continuously from positive symptoms to negative symptoms | r = .18 | Only positive and only negative symptoms with lower thickness |
| Macular volume cube left eye | r = -.66 | Volume decreases continuously from positive symptoms to negative symptoms | r = .09 | Only positive and only negative symptoms with lower thickness |
| Thickness subfield right eye | r = -.65 | Volume decreases continuously from positive symptoms to negative symptoms | r = .40 | Only positive and only negative symptoms with lower thickness |
| Thickness subfield left eye | r = .34 | Only positive and only negative symptoms with lower thickness | r = .18 | Only positive and only negative symptoms with lower thickness |
| Volume cube right eye | r = -.56 | Volume decreases continuously from positive symptoms to negative symptoms | r = .19 | Only positive and only negative symptoms with lower thickness |
| Volume cube left eye | r = -.58 | Volume decreases continuously from positive symptoms to negative symptoms | r = .26 | Only positive and only negative symptoms with lower thickness |
| Thickness average cube right eye | r = -.57 | Volume decreases continuously from positive symptoms to negative symptoms | r = .23 | Only positive and only negative symptoms with lower thickness |
| Thickness average cube left eye | r = -.65 | Volume decreases continuously from positive symptoms to negative symptoms | r = .09 | Only positive and only negative symptoms with lower thickness |

SSD = schizophrenia spectrum disorder.

controls, individuals with acute and chronic schizophrenia spectrum disorder (SSD) showed specific alterations in the retinal nerve fiber layers (RNFL). Among individuals with acute SSD, a longer disease duration was associated with larger RNFL indices, while among individuals with chronic SSD, a longer disease duration was associated with smaller RNFL indices. In both acute and chronic SSD, either positive or negative symptoms (as opposed to prevalently positive or prevalently negative symptoms) were associated with smaller RNFL indices; symptomatology and RNFL indices were associated in a non-linear fashion. Overall, the present pattern of results adds to the current literature in an important way, showing that the use of Optical Coherence Tomography (OCT) to assess RNFL indices allowed a sophisticated analysis of neuronal changes in individuals with SSD. In addition,

disease duration and disease symptomatology were associated in complex, non-linear (or even cubic) ways.

Two hypotheses and one research question were formulated and each of these is considered in turn.

Our first hypothesis was that, compared to healthy controls, individuals with SSD would have smaller RNFL indices, including macular volume and macular thickness. This was not fully supported. As shown in Tables 1–5, mean differences in RNFL indices between typically developed adults and individuals with acute and chronic SSD were small and inconsistent. Importantly, only individuals with acute SSD had smaller RNFL indices when compared to typically developed adults and individuals with chronic SSD. In this respect we were able only partially to replicate some previous findings (Ascaso et al., 2010, 2015; Schönfeldt-Lecuona et al., 2016, 2019). On the other hand, our results appear to be in line with those reported by Chiu et al. (2012): no mean differences of RNFL indices between individuals with SSD and healthy controls; and by Lee et al. (2013): inconsistent findings as regards RNFL indices in individuals with SSD and healthy controls. Likewise, the present findings differ from those reported by Ascaso et al. (2015). In their study, compared to healthy controls, individuals with SSD had smaller RNFL indices than healthy controls, and this was particularly apparent in individuals with chronic as opposed to acute SSD.

The findings from the present study are not consistent with the view that SSD is a neurodegenerative disease, as volume differences between healthy controls and individuals with SSD were spurious. However, a closer look at the means and standard deviations (Tables 1–5) also shows that RNFL indices had a large range of variability. It is therefore also possible that particularly small and particularly large RNFL indices in both healthy controls and participants with SSD obscured a clearer pattern of results. Such methodological issues have been mentioned elsewhere (Kazakos and Karageorgiou, 2020; Silverstein et al., 2019).

Our second hypothesis was that RNFL indices would be smaller with longer disease duration. This was confirmed exclusively for individuals with chronic SSD, while for individuals with acute SSD, exactly the opposite association was observed. In this respect our results only partially match findings reported elsewhere (Lee et al., 2013; Schönfeldt-Lecuona et al., 2019). Importantly, as shown in Table 6 and Figs. 2–5, associations were unbiased; that is to say, outliers did not bias correlation coefficients and regression lines. In line with this, non-linear (quadratic) and cubic correlations (see Fig. 5) reflected the pattern of associations between RNFL indices and disease duration in much more accurate fashion. Furthermore, this pattern of association points to an acceleration of neurodegeneration (Silverstein et al., 2019) or failed neuro-regeneration (Falkai et al., 2015) in individuals with chronic SSD.

The following issue remains. It is difficult to explain the observation that, among individuals with acute SSD, a longer disease duration was associated with a larger RNFL indices (Table 6, Figs. 2 and 3). This pattern is in contrast to previous findings (Lee et al., 2013; Schönfeldt-Lecuona et al., 2019). A highly speculative possibility is that, among individuals with acute SSD, a process of neuroregeneration occurs with increasing disease duration. Longitudinal data or the follow-up of the present individuals with SSD could help to clarify this by investigating associations between disease progress and RNFL indices.

The research question considered the extent to which dimensions of RNFL are associated with current positive and negative symptoms of SSD. Again, no simple, uniform and linear answer emerged. Both exclusively positive and exclusively negative symptoms (as opposed to rather positive or rather negative symptoms) were associated with smaller RNFL indices (but more so among individuals with chronic SSD; in contrast, among individuals with acute SSD, smaller RNFL indices were associated with more pronounced negative symptoms). These non-linear associations were unexpected. Again, neither the present data nor the current literature in the field offer appropriate explanations. It appears that among individuals with (chronic) SSD and mixed symptomatology (rather positive symptoms with some negative symptoms; rather negative symptoms with some positive symptoms) RNFL indices are

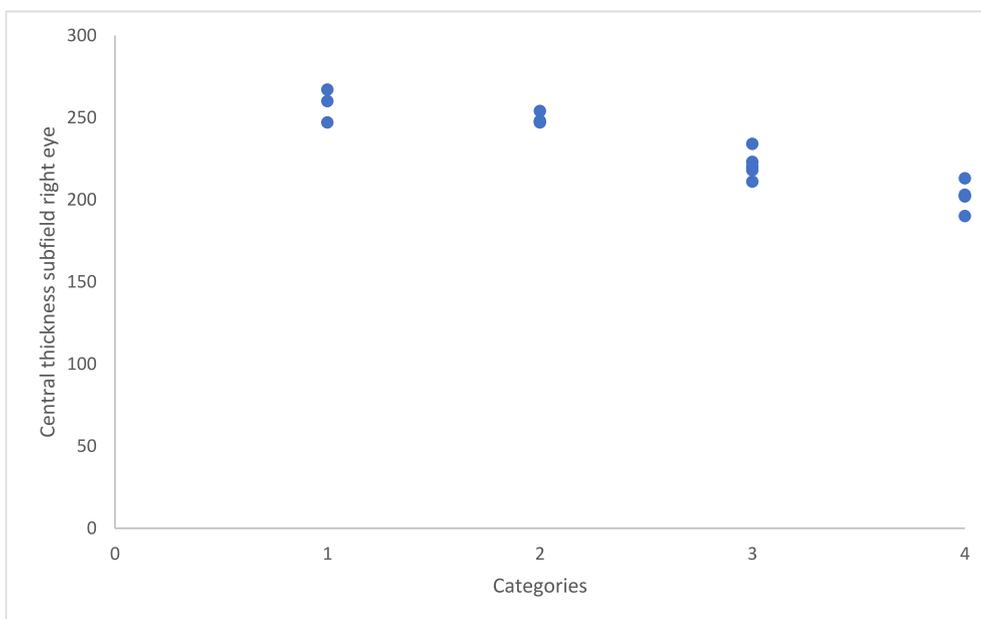


Fig. 6. Non-linear association between central thickness subfield of the right eye and symptom categories among participants with acute schizophrenia; 1 = only positive symptomatology; 2 = prevalently positive and negative symptomatology; 3 = prevalently negative and positive symptomatology; 4 = only negative symptomatology. $R = -0.65$.

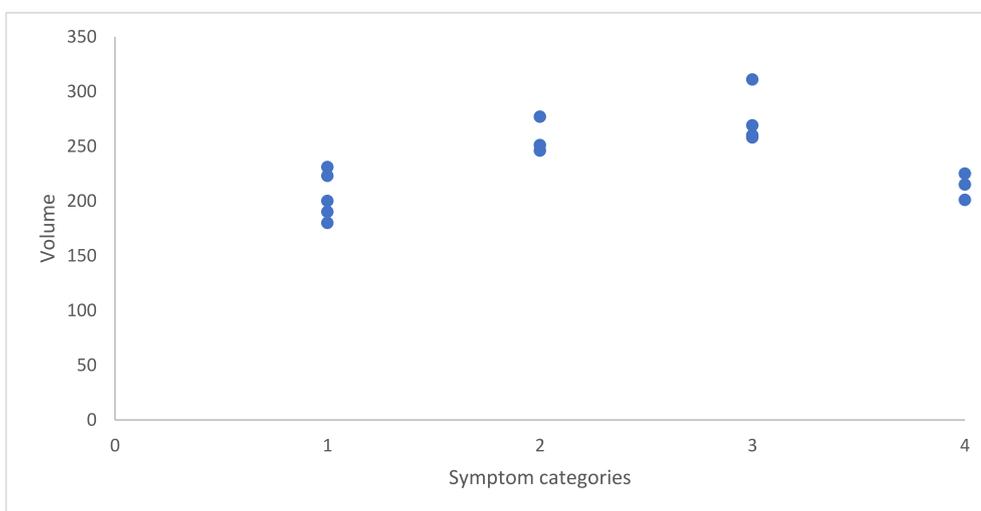


Fig. 7. Non-linear association between symptom characteristics and volume of the central and subfoveal macula thickness (right eye) among participants with chronic schizophrenia spectrum disorder. 1 = only positive symptomatology; 2 = prevalently positive and negative symptomatology; 3 = prevalently negative and positive symptomatology; 4 = only negative symptomatology. $R = 0.40$.

larger. It is therefore possible that individuals with both negative and positive symptomatology and larger RNFL indices have more favorable disease outcomes. However, we are unaware of any evidence to support this in the current literature.

The novelty of the study results should be balanced against the following limitations. First, the sample sizes might be considered rather small, though we did rely on effect size calculations, which are not sensitive to sample sizes. Second, we focused on symptoms of schizophrenia, while other important domains of behavior and functioning such as cognitive performance, social interactions with family members or in the workplace were not assessed. Likewise, third, the cross-sectional nature of the data is unable to provide a comprehensive and more robust answer to the key question, namely the extent to which SSD should be considered either a neurodegenerative disease, or failed neuronal regenerative disease, thus leaving the possibility of neuronal

repair and regeneration or both (Falkai et al., 2015). On this point, it would be important to assess RNFL dimensions in persons with SSD at different treatment points and particularly those in full remission, partial remission, response and non-response. Such a study design would allow a more accurate estimation of the degree to which treatment success (or failure) is associated with structural changes in the RNFL and by extension with morphological changes in the brain. Given this, a follow-up psychiatric and RNFL-related assessment of the present individuals with SSD could provide a deeper knowledge of both disease progression and neuro-degeneration. Fourth, we assessed males with SSD who were willing and able to participate in the study. It follows that the sample might be biased, and that the present results cannot be generalized to females with SSD. Last, from a statistical point of view, there is a risk of model overfitting, particularly considering the complex non-linear models. However, we believe that non-linear models offer an

excellent opportunity to explore previously unobserved and unexpected patterns of associations in the field of schizophrenia.

5. Conclusions

Optical coherence tomography (OCT) to assess RNFL indices is an easy and non-invasive means of assessing neurological morphological indices. Among individuals with acute and chronic SSD RNFL indices, disease duration and symptomatology were associated in a complex and non-linear fashion.

Author statement

All authors declare that they were substantively involved in the setup of the study, in working on the data and in drafting and writing the final and the revised version of the manuscript.

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Declaration of competing interest

All authors declare no conflicts of interest.

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