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Optical coherence tomography indices of structural retinal pathology in schizophrenia

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Abstract

Background. Prior optical coherence tomography (OCT) studies of schizophrenia have identified thinning of retinal layers. However, findings have varied across reports, and most studies have had serious methodological limitations. To address unresolved issues, we determined whether: (1) retinal thinning in schizophrenia occurs independently of comorbid medical conditions that affect the retina; (2) thinning is independent of antipsychotic medication dose; (3) optic nerve parameters are abnormal in schizophrenia; and (4) OCT indices are related to visual and cognitive impairments common in schizophrenia.

Methods. A total of 32 people with schizophrenia and 32 matched controls participated. Spectral domain OCT generated data on retinal nerve fiber layer (RNFL), macula, and ganglion cell-inner plexiform layer (GCL-IPL) thickness, in addition to cup volume and the cup-to-disc ratio at the optic nerve head. Subjects with schizophrenia also completed measures of symptoms, visual processing, and IQ.

Results. The groups did not differ on RNFL, macula, or GCL-IPL thickness. However, thinning of these layers was related to the presence of diabetes or hypertension across the sample as a whole. The schizophrenia group demonstrated enlarged cup volume and an enlarged cup-to-disc ratio in both eyes, which were unrelated to medical comorbidity, but were related to increased cognitive symptoms.

Conclusions. Past reports of retinal thinning may be artifacts of medical comorbidity that is over-represented in schizophrenia, or other confounds. However, optic nerve head abnormalities may hold promise as biomarkers of central nervous system abnormality, including cognitive decline, in schizophrenia.

Introduction

The retina is a part of the central nervous system (CNS), with both it and the brain developing from the anterior part of the neural tube early in development. Because of this, the retina has been viewed as a 'window to the brain' (Chu *et al.* 2012; London *et al.* 2013; Jindal, 2015; Schonfeldt-Lecuona *et al.* 2016) in terms of their many similarities in structure, neurotransmitters, and function. Data supporting this view come from studies, in multiple conditions, indicating that thinning of neural layers of the retina predicts cortical atrophy and other disease characteristics. For example, thinning of the axon layer of retinal ganglion cells (i.e. the retinal nerve fiber layer or RNFL; see Fig. 1) is related to brain volume loss, illness progression and cognitive decline in multiple sclerosis (MS) (Gordon-Lipkin *et al.* 2007; Pulicken *et al.* 2007; Toledo *et al.* 2008) and Alzheimer's disease (AD) (Iseri *et al.* 2006; Liu *et al.* 2015; Ferrari *et al.* 2017). RNFL thinning is also related to brain volume loss in aging (Ong *et al.* 2015). In addition, RNFL thinning is related to the severity of visual hallucinations and functional decline in Parkinson's Disease (Lee *et al.* 2014; Satue *et al.* 2014). Because retinal ganglion cell axons form the optic nerve, leave the retina, and synapse at the lateral geniculate nucleus (LGN), where they provide segregated input to the subcortical magnocellular (M) and parvocellular (P) visual pathways, examination of retinal structure may be especially relevant to schizophrenia, where impairments in both pathways, but especially the M system, have often been reported (Butler *et al.* 2008; Lalor *et al.* 2012; Jahshan *et al.* 2017).

Examination of the thickness of the RNFL and other retinal layers is typically achieved using optical coherence tomography (OCT). OCT is a non-contact retinal structural imaging technique in which infrared light is projected both into the eye and to a reference mirror. The difference between the spectral frequency composition of light reflected back from the eye (i.e. the original spectral frequency profile minus what was absorbed by retinal structures), in comparison with the unaltered light spectra reflected back from the reference mirror, is used to reconstruct images of retinal layers, in a manner analogous to that used by ultrasound. Examples of typical pseudocolorized (to differentiate layers) OCT images, of the RNFL and

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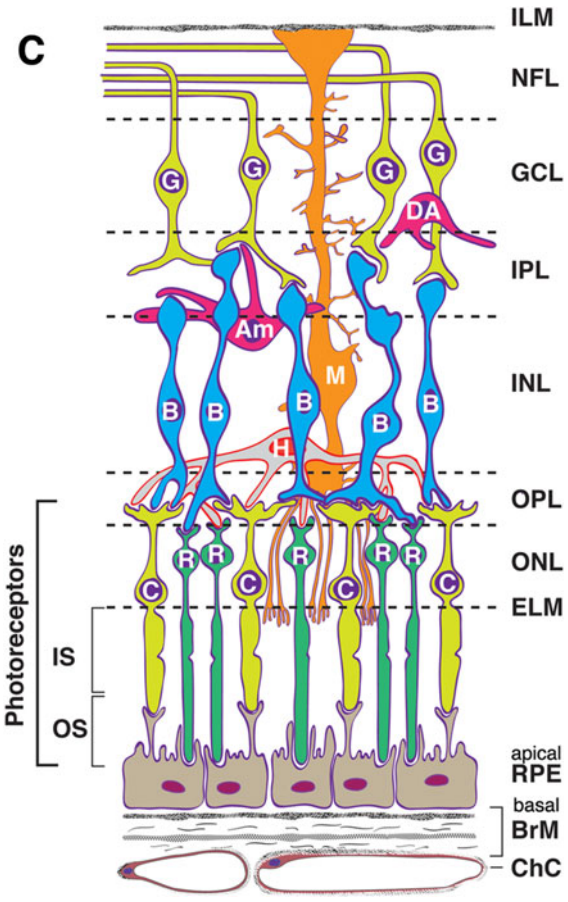

Fig. 1. Illustration of retinal cell types and layers. Cells: RPE, retinal pigment epithelium (support to photoreceptors); C, cone photoreceptor; R, rod photoreceptor; H, horizontal cell (interneuron); B, bipolar cell (interneuron); M, Müller cell (radial glial cell); Am, amacrine cell (interneuron); DA, displaced amacrine cell (interneuron); G, ganglion cell (output neuron). Müller cells (M) form the ELM, and their foot processes partially form the ILM. Layers: ChC, choriocapillaris (capillary bed for RPE and photoreceptors); BrM, Bruch's membrane (vessel wall and RPE substratum); ELM, external limiting membrane (junctional complexes); ONL, outer nuclear layer; OPL, outer plexiform layer (synapses); INL, inner nuclear layer; IPL, inner plexiform layer (includes ganglion cell dendrites, bipolar cell axons, and amacrine cells); GCL, ganglion cell (body) layer; NFL, nerve fiber layer (ganglion cell axons); ILM, inner limiting membrane. Image, and the majority of the figure caption reproduced from Fig. 2c in: Zheng W, Reem RE, Omarova S, Huang S, DiPatre PL, *et al.* (2012) Spatial Distribution of the Pathways of Cholesterol Homeostasis in Human Retina. PLOS ONE 7(5): e37926. https://doi.org/10.1371/journal.pone.0037926 via a Creative Commons Attribution (CC BY) license.

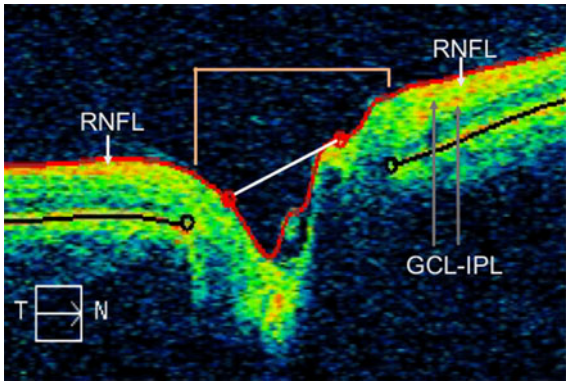

Fig. 2. Horizontal tomogram indicating regions assessed by RNFL scans, in this case for the left eye of a study subject: inner limiting membrane (ILM; red line); RNFL (orange area just beneath ILM); GCL and IPL layers (beneath RNFL); optic disc (area indicated by width of tan lines near top, and also by the distance between the black circles within the image); cup boundaries (indicated by white line between the two red circles on the red ILM line). The cup-to-disc ratio is the width of the cup divided by the width of the disc. T, temporal; N, nasal.

macula respectively, are presented in Figs 2 and 3. In addition to thickness of the RNFL near the optic nerve head, and of the macula (through all layers anterior to the retinal pigment epithelium), both of which are two-dimensional (2-D) measurements (i.e. of length), volumetric (3D) measurements are possible, such as macular volume which is commonly referred to in the OCT literature as macular cube volume, within a pre-specified range of coordinates. Several other OCT metrics are also useful and commonly reported. These include the thickness of the retinal ganglion cell body layer (GCL, the cells whose axons form the RNFL), and of the inner-plexiform layer (IPL) which consists of the ganglion cell dendrites, bipolar cell axons, and amacrine cell neuritic processes that subserve lateral connections between ganglion cells. The thickness of the combination of these layers (GCL-IPL) is typically reported, and we follow that convention here. Measurements at the optic nerve head are also informative. For example, cup volume (see Fig. 2) often reflects the overall size of the optic nerve, and cup-to-disc ratio, when enlarged, can reflect a number of issues including neural tissue loss, vascular abnormalities, inflammation, or an enlarged optic nerve, issues that are common in retinal diseases (Chen *et al.* 2015; Scripsema *et al.* 2016; Geyman *et al.* 2017; Mo *et al.* 2017). A final OCT variable we report on is RNFL symmetry, which is the degree to which RNFL thickness is similar across the two eyes. Deviations from symmetry typically reflect some form of optic neuropathy (Budenz, 2008). Data generated with OCT scans are virtually identical to those generated from histologic examination of retinal tissue (Ghazi *et al.* 2006; Vajzovic *et al.* 2012), and are highly reliable, with intraclass correlations from repeated measurements exceeding 0.99 (Wadhwani *et al.* 2015).

OCT studies of schizophrenia generally indicate RNFL or macula thinning (Silverstein & Rosen, 2015). However, not all studies have demonstrated these effects, and many of the studies with positive findings are characterized by potential confounds or serious methodological limitations. For example, in a study from Spain, (Ascaso *et al.* 2010) reported RNFL but not macula thinning in schizophrenia. However, their sample consisted of only 10 patients and 10 controls, and none of the findings would have been statistically significant if the p values were adjusted for multiple comparisons [e.g. on the 5 RNFL comparisons alone (4 quadrants plus the overall thickness), the lowest uncorrected p value was 0.047]. Also, while subjects with observable retinal pathology were excluded, subjects with diseases that are overexpressed (Liao *et al.* 2011), and typically untreated (Nasrallah *et al.* 2006) in schizophrenia and that can also cause subtle retinal changes (e.g. diabetes and hypertension) were not excluded. A follow-up study from this group (Cabezon *et al.* 2012), with 30 patients and 30 controls, reported RNFL but not macula thinning, and enlarged cup-to-disc ratio and cup volume. This study, however, only investigated the right eye (precluding the built-in chance for replication afforded by studying both eyes), and the data were presented in a published conference abstract only, not in a peer-reviewed article. In another study from this group (Ascaso *et al.* 2015) with 30 schizophrenia patients and 30 controls, the patient group was characterized by

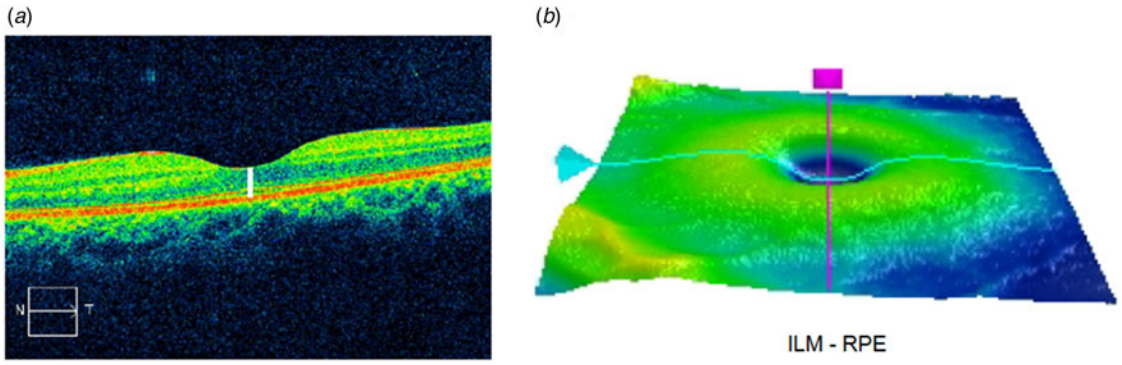

Fig. 3. (*a*) OCT image generated by macula scan. The vertical white line has been added to demonstrate the depth of the scan, from the inner limiting membrane (ILM) at the top to the retinal pigment epithelium (RPE; in red, beneath the photoreceptor layer). (*b*) Topographic map showing the region of the macula scan. Scan depth indicated by concavity in blue line at the position of the scan axis (purple line).

RNFL thinning, but the between-group difference was only significant for the right eye. In contrast, significant macula thinning was observed only in the left eye. Significant differences from controls were found only for the patient subgroup that had not had a psychotic episode within the past 6 months, suggesting that acute psychosis may be associated with inflammation and tissue swelling that prevents detection of retinal atrophy. However, the limitations of findings to specific eyes, the differences between findings in each eye, and the divergence of these findings from other studies once again raises questions about the robustness and validity of OCT findings in schizophrenia. Moreover, potential confounds with this study were that: (1) it is not clear whether potential subjects with relevant comorbidity were excluded (e.g. subjects with diabetic retinopathy were excluded, but it is not clear whether subjects with diabetes alone were excluded); and (2) the patient group was on an average dose of antipsychotic medication (chlorpromazine equivalent dose = 711.6 ± 490.6 mg/day) that was at the upper end of what is observed worldwide (Gardner *et al.* 2010). The latter is important because one potential consequence of antipsychotic medication use is the blockade of retinal dopamine (DA) receptors, which can lead to death of ganglion and other retinal cells (since all retinal cell types have DA receptors), due to reduced activity – all of which could contribute to thinning of retinal layers (Silverstein & Rosen, 2015). This is similar to what is observed in MDTP treated monkeys (Ghilardi *et al.* 1988), and in humans with Parkinson's disease (Yu *et al.* 2014), where reduced input due to loss of DA-containing amacrine cells is thought to lead to loss of axons and cell bodies in other retinal cells (Inzelberg *et al.* 2004).

A study from Malaysia (Lee *et al.* 2013) also reported reduced RNFL (overall, and in 3 of 4 quadrants) and macula thickness in 30 schizophrenia patients compared to 30 healthy controls. Interestingly, this effect was observed only in patients with longer duration of illness, while those with less than 2 years since illness onset did not differ from controls. However, a confound in this study was that while the patient and control groups were age-matched overall, the older and more chronically ill patient subgroups were compared with the control group as a whole, not to an age-matched subgroup of controls. Therefore, while the authors emphasized the potential effects of illness progression on retinal thinning (which could also be due to longer-term antipsychotic medication use), it is also possible that the effects are due to normal aging, since it is known that aging is associated with retinal thinning (Harwerth *et al.* 2008; Harwerth & Wheat, 2008). Support for this comes from the study by Ascaso *et al.* (2015) that found no relationship between illness chronicity and any OCT variable after correcting for age.

Celik *et al.* (2016) reported on a study from Turkey of 81 schizophrenia patients and 41 healthy controls. In this study, the schizophrenia group demonstrated thinning of the RNFL overall, and in 2 RNFL segments. RNFL thickness was not related to treatment-refractory *v.* responsive status, but the thickness of the choroid at the macula was reduced in the treatment-refractory group (but not in patients overall relative to controls). Data on macula thickness was not reported. Importantly, none of the findings from this study would survive correction for multiple statistical comparisons. In addition, the antipsychotic medication dose of patients was not reported. Another study from Turkey (Yilmaz *et al.* 2016) compared 34 patients and 30 controls. This study reported a significant degree of RNFL thinning, overall and in the nasal quadrant, and macula thinning in two quadrants, and these findings survived a Bonferroni correction for multiple comparisons. No data on medication usage were reported for the patients, however. In contrast to all of these studies, a study from the UK of 49 patients and 40 controls (Chu *et al.* 2012) reported normal RNFL and macula thickness values in schizophrenia, overall and in all segments. This study used an older form of OCT, time domain OCT (TD-OCT), whereas all other studies used the newer, faster and higher resolution technique of spectral domain OCT (SD-OCT). On the other hand, TD-OCT has been used in many research studies in ophthalmology over many years and it is clearly able to detect retinal pathology when it exists. Therefore, we consider it unlikely that the negative findings from Chu *et al.* are solely equipment-related.

Taken together, these studies raise several questions. One is whether retinal layer thinning in schizophrenia can be observed independently of comorbid medical conditions such as diabetes and hypertension. Another question is whether retinal layer thinning would be observed in chronically ill patients on normative or low doses of antipsychotic medication. Also, given evidence of other retinal abnormalities in neuropsychiatric disorders, such as enlargement of the cup-to-disc ratio at the optic nerve head (see Fig. 2) (Tsai *et al.* 1991; Syc *et al.* 2011), and the suggestion from a single published abstract (see above) that this abnormality may be present in schizophrenia, a question is whether this index is indeed abnormal in schizophrenia, and if so, whether it is related to loss of retinal tissue. Finally, given the well-documented visual processing abnormalities in schizophrenia [reviewed in

(Silverstein, 2016)], there remains the unanswered question of the extent to which these reflect retinal impairment (Silverstein & Rosen, 2015). The goal of this study was to address each of these questions.

Method

Subjects

Participants were 32 people with schizophrenia (SZ) (19 male) and 32 psychiatrically healthy controls (CON) (18 male), between the ages of 21 and 60. The groups were matched, at the group level, on age and gender. Within each group, 21 subjects were free of medical comorbidity that can affect retinal health (e.g. diabetes, hypertension) (Sz-DH and Con-DH subgroups) and 11 subjects had documented diabetes or hypertension (Sz + DH and Con + DH subgroups). All subjects were free of retinal or other eye injury or disease (e.g. cataracts, macular degeneration, diabetic retinopathy, glaucoma), as documented by medical records and by slit lamp biomicroscopy of the retina, conducted by an ophthalmologist (SG) as part of this study. All subjects were also free of neurological disorders, intellectual and developmental disorders (e.g. autism), active substance abuse disorders for at least 6 months, and a history of head injury with loss of consciousness of more than 10 min. All subjects provided written informed consent. The study was approved by the IRB at Rutgers Biomedical and Health Sciences.

Clinical assessment

Diagnoses of schizophrenia were confirmed by trained and experienced research assistants using the Structured Diagnostic Interview for DSM-IV, Patient Version (First *et al.* 2002). Control subjects self-reported no history of DSM-IV Axis-I disorders. For the patient group, symptom severity for the past 2 weeks was assessed using the Positive and Negative Syndrome Scale (Kay *et al.* 1987), which was scored using a five-factor model consisting of positive, negative, cognitive†[1], depression and excitement syndromes (Lindenmayer *et al.* 1994*a*, *b*). The overall level of functioning of patients was assessed with the Multidimensional Scale of Independent Functioning (MSIF) (Jaeger *et al.* 2003). The current level of cognitive functioning in patients was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI-II) (Wechsler, 2011).

OCT

OCT data were acquired with a Cirrus 4000 HD-OCT scanner, which is an SD-OCT device. Data were acquired at a scan depth of 2 millimeters, with a resolution of 5 micrometers, at a rate of over 27 000 axial (A-) scans per second. Data were processed, in terms of layer segmentation, and thickness and volume values, using Cirrus software version 8.1.0.117. Macular and RNFL scans were acquired for each eye separately. GCL-IPL images were generated based on macular scan data. Prior to OCT scans, subjects' pupils were pharmacologically dilated. For each eye, we report on: overall RNFL thickness as well as thickness of each RNFL quadrant (superior, inferior, nasal, temporal); symmetry of average RNFL values across the two eyes; macula central subfield (CSF) thickness, macula average thickness (including the CSF, intermediate regions bordering the CSF, and the 4 outer quadrants), macula volume (a 3D metric); GCL-IPL thickness; optic cup volume; and cup-to-disc ratio.

Visual assessment

Prior to the OCT session, all subjects were tested for visual acuity using a logarithmic acuity chart. Patients were also tested with: (1) a computerized contrast sensitivity task (Deveau *et al.* 2014), from which peak (spatial frequency) and mean contrast sensitivity were recorded; (2) a contour integration test (Silverstein *et al.* 2012); (3) a test assessing sensitivity to spatial frequency manipulation in facial images requiring gender discrimination (Silverstein *et al.* 2010); and (4) a test of size constancy (Silverstein *et al.* 2013). All of these tests measure functions that have been shown to be impaired in schizophrenia, and so their inclusion was to determine whether evidence of retinal structural impairment was related to performance on these tasks.

Data analysis

Differences between the two primary groups, and between the four subgroups, on OCT variables, were analyzed using the general linear model/univariate analysis of variance (ANOVA) procedure in SPSS 24. Effect sizes (η_p^2), are reported (in Tables 2 and 3) in all cases. When a significant difference was observed in the analyses with the four subgroups, post-hoc Scheffé tests were used to probe for between-subgroup pairwise differences. Correlations between OCT indices and scores on other measures were explored using Spearman's Rho correlations. Group differences in demographic variables were explored using chi-square and ANOVA.

Results

Demographic data

Demographic data are presented in Table 1. The two primary groups (i.e. SZ, CON) did not differ in age [$t(62) = -0.48$, $p = 0.64$] or gender [$\chi^2(1) = 0.064$, $p = 0.80$]. However, when the four subgroups were considered there was a significant group difference in age [$F(3,63) = 6.18$, $p = 0.001$], with the Sz + DH group being older than the SZ-DH and CON-DH groups ($ps = 0.002$ and 0.012, respectively) based on post-hoc Scheffé tests.

OCT data

Means, standard deviations, and p values for group comparisons on RNFL, macula, GCL-IPL, and cup-to-disc ratio data are presented in Table 2. The two primary groups did not differ significantly on any RNFL variables (even without correction for multiple comparisons), including overall RNFL thickness, the thickness of any quadrant, and RNFL symmetry. Similarly, when the four subgroups were compared, there were no significant differences on any RNFL variables.

The two primary groups also did not differ significantly on macula CSF. The SZ group was characterized by trend level (using uncorrected p values only) thinning on measures of macula cube thickness and total macula cube volume, for both eyes. When the outer quadrants of the macula were examined, the SZ group demonstrated significant thinning of the left nasal region and a trend towards thinning of the right nasal region. When

†The notes appear after the main text.

Table 1. Demographic data

		All subjects		Medically unaffected		Diabetes/hypertension	
		SZ	CON	Sz-DH	Con-DH	Sz + DH	Con + DH
Age	Mean (SD)	40.46 (12.09)	39.19 (11.03)	35.14 (11.07)	37.67 (9.07)	50.91 (5.32)	42.09 (14.10)
Sex	Male	19	18	13	11	6	7
	Female	13	14	8	10	5	4

the four subgroups were compared on the same variables, there were significant group differences in all cases except for left and right macula inferior quadrants. Post-hoc Scheffé tests indicated that in all cases except one where the subgroup difference was significant, this was due to the Sz + DH group having lower thickness values than both the Sz-DH and Con-DH groups. This may be an age effect, however, as the SZ + DH group was the oldest of the four subgroups, and the CON + DH group did not demonstrate thinning relative to either the Sz-DH or Con-DH groups.

The two primary groups did not differ in either GCL-IPL mean thickness or minimum thickness in either the left or right eye. When the four subgroups were compared on the same variables, there were two cases where the Sz + DH group was characterized by thinner values than the Con-DH group only.

Striking differences were observed, however, on the variables of cup volume and cup-to-disc ratio. Here, the primary groups differed significantly on both variables, for both eyes. In some cases, the mean values for the SZ group were double that of the CON group (see Table 2). When the four subgroups were compared, the main effect of group was significant for the cup-to-disc ratio for both eyes, and at the trend level for cup volume for both eyes. While in every case the two patient subgroups had larger (i.e. more abnormal) values than the two control subgroups, post-hoc comparisons were not significant between any of the group pairs.

A final set of tests compared those subjects with diabetes or hypertension *v.* those without, regardless of whether they had schizophrenia. These data are presented in Table 3. In many cases, the medically affected group demonstrated thinning of retinal structures. This included left (but not right) eye RNFL, all macular thickness, and volume variables, most outer macular quadrants, GCL-IPL average thickness in both eyes, and GCL-IPL minimum thickness in the left eye (with a trend level finding for the right eye).

Relationships between OCT findings and visual function, symptoms, community functioning and medication dose (patient data only)

To reduce the number of tests and Type I error, for these sets of analyses (with the exception of correlations with medication, see below) we limited the OCT variables to cup volume, and cup-to-disk ratio, since these were the only indices on which the two primary groups differed. However, correlations were run for data from both eyes to serve as a preliminary check on the replicability of any significant finding. There were no cases where these variables correlated significantly or at a trend level with the visual task (e.g. contrast sensitivity, contour integration, sensitivity to spatial frequency manipulation, or size constancy), WASI-II, or MSIF scores for both eyes. In terms of symptoms, significant or trend level relationships were observed between PANSS Cognitive factor scores and: left cup-to-disc ratio (r = 0.34, p = 0. 07), right cup-to-disc ratio (r = 0.41, $p < 0.05$), and left and right eye cup volumes (rs = 0.48 and 0.45, ps = 0.01 and 0.02), respectively. Relationships with other symptom dimensions were not significant.

The mean daily CPZ equivalent dose of antipsychotic medication for the patient group was 462 mg (5% trimmed mean = 408; median = 391). Correlations with CPZ equivalent dose were examined with the variables of mean RNFL, macula CSF, cup-to-disc ratio, and cup volume, for the right and left eyes. Correlations with left and right RNFL thickness were not significant: (rs = −0.25 and −0.05, ps = 0.19 and 0.81, respectively). Similarly, correlations with left and right macula CSF were not significant (rs = 0.04 and 0.08, ps = 0.84 and 0.68, respectively). However, there were significant positive relationships between medication dose and cup volume for both the left and right eye (rs = 0.41 and 0.39, $ps < 0.05$). Correlations with cup-to-disc ratio were not significant (rs = 0.05 and 0.04, ps = 0.80 and 0.83).

Discussion

Our findings suggest that past reports of RNFL and macula thinning in schizophrenia overestimate their prevalence and severity. In this study, when medical comorbidity and age were eliminated as confounds, patients and psychiatrically healthy control subjects did not differ on a range of RNFL or macula variables. In contrast, across all subjects, the presence of diabetes or hypertension, conditions that can cause retinal thinning and that are over-represented and often untreated in schizophrenia, was consistently associated with, and presumably the cause of, RNFL and macula thinning.

Further support for the validity of our findings comes from data on healthy controls in several studies that used the same OCT scanning device that we used (Cirrus 4000). For example, (Vizzeri *et al.* 2009) reported a mean RNFL thickness of 89.80 microns with a confidence interval of ±3.2. This is very close to our SZ means of 89.31 (left eye) and 87.37 (right eye), and CON group means of 87.47 (L) and 89.38 (R). The means for the Sz-DH (92.86 left; 89.90 right) and Con-DH (88.05 left; 89.76 right) groups were also close to the mean reported by Vizzeri *et al.* (see Table 2). Similar results were reported by (Wadhwani *et al.* 2015) (mean = 93.62) and (Knight *et al.* 2009) (mean = 92.00). These values agree with the normative RNFL mean of 93.00 published by Cirrus[2]. If indeed our data indicate normal RNFL and macula thickness in schizophrenia, it raises the possibility that the abnormal, but often inconsistent, findings reported in past studies are due to medical comorbidity, age effects, failure to control for multiple statistical tests (as discussed in the Introduction), and/or to the use of different OCT scanners and/or different retinal layer segmentation algorithms, which can vary in their findings (Warner *et al.* 2011). It is also possible that, as noted in the Introduction, differences across studies could

Table 2. Means (SDs) of study variables for the two primary groups, and four subgroups. Column 4 displays the p values and effect sizes for the primary between-group comparisons (SZ v. CON). Column 9 displays p values and effect sizes for the four subgroup comparisons. In cases where the ANOVA revealed a significant difference between the four groups, post-hoc Scheffé tests were used to explore pairwise differences. Significant post-hoc test results are indicated in the row under the means and SDs for the four subgroups, with the p value associated with the significant pairwise difference under the groups that differed from each other

	All subjects			Medically unaffected		Diabetes/hypertension		
	SZ	Con	$p\|\eta_p^2$	Sz-DH	Con-DH	Sz + DH	Con + DH	$p\|\eta_p^2$
Right RNFL	87.37 (19.96)	89.38 (11.68)	0.63|0.004	89.90 (23.20)	89.76 (11.60)	82.55 (10.96)	88.64 (12.35)	0.64|0.028
Left RNFL	89.31 (10.77)	87.47 (12.40)	0.53|0.006	92.86 (10.37)	88.05 (12.50)	82.55 (8.20)	86.36 (12.71)	0.09|0.100
Right superior RNFL	111.13 (16.43)	104.22 (24.98)	0.20|0.027	115.76 (15.73)	103.43 (29.29)	102.27 (14.53)	105.73 (14.67)	0.20|0.174
Left superior RNFL	113.59 (16.16)	110.66 (17.80)	0.49|0.008	118.52 (15.17)	110.38 (18.28)	104.18 (14.17	111.18 (17.71)	0.13|0.090
Right inferior RNFL	117.06 (19.98)	118.59 (23.18)	0.78|0.001	122.81 (14.89)	118.00 (20.98)	106.09 (24.35)	119.73 (28.00)	0.21|0.070
Left inferior RNFL	117.75 (16.59)	114.97 (23.69)	0.59|0.005	122.38 (15.55)	115.81 (22.95)	108.91 (15.46)	113.86 (26.12)	0.32|0.057
Right temporal RNFL	60.53 (10.01)	59.97 (9.93)	0.82|0.001	62.67 (11.12)	60.10 (9.41)	56.45 (5.96)	59.73 (11.33)	0.41|0.046
Left temporal RNFL	60.25 (9.90)	56.25 (9.76)	0.11|0.041	63.05 (9.92)	56.33 (9.17)	54.91 (7.70)	56.09 (11.28)	0.06|0.118
Right nasal RNFL	71.66 (13.20)	71.66 (14.43)	1.00|0.000	74.81 (12.64)	73.19 (14.83)	65.64 (12.64)	68.73 (13.83)	0.27|0.063
Left nasal RNFL	65.91 (13.64)	65.84 (14.95)	0.99|0.000	67.71 (13.17)	66.52 (14.50)	62.45 (14.48)	64.55 (16.43)	0.78|0.018
RNFL symmetry	86.19 (10.18)	82.34 (15.93)	0.25|0.021	88.14 (8.37)	80.81 (19.19)	82.45 (12.56)	85.27 (5.95)	0.34|0.054
Right macula CSF	245.00 (24.65)	252.78 (28.68)	0.25|0.021	250.19 (22.10)	259.24 (29.91)	235.09 (27.24)	240.45 (22.50)	0.06|0.114
Left macula CSF	246.72 (27.08)	253.47 (28.51)	0.34|0.015	249.49 (21.91)	262.24 (27.82)	241.45 (35.59)	236.73 (22.49)	0.05|0.121
Right macula volume	9.74 (0.88)	10.05 (0.58)	0.10|0.043	10.05 (0.59)	10.18 (0.55)	9.12 (1.07)	9.82 (0.76)	0.001*|0.225
				0.01*	0.003*	0.01*/0.003*		
Left macula volume	9.62 (0.85)	9.98 (0.63)	0.053|0.059	9.95 (0.61)	10.13 (0.59)	8.97 (0.89)	9.71 (0.63)	<0.001*|0.283
				0.003*	<0.001*	0.003*/<0.001		
Right macula average	270.28 (24.48)	279.22 (15.94)	0.09|0.046	278.76 (16.47)	282.57 (15.46)	254.09 (29.58)	272.82 (15.54)	0.001*|0.029
				0.01*	0.002*	0.01*/0.002*		
Left macula average	267.09 (23.70)	277.31 (17.34)	0.05|0.059	276.33 (17.37)	281.43 (16.17)	249.45 (24.83)	269.45 (17.48)	<0.001*|0.279
				0.003*	<0.001*	0.003*/<0.001		
Right outer macula superior	273.16 (17.83)	277.59 (14.00)	0.27|0.019	279.38 (16.11)	280.62 (12.38)	261.27 (15.15)	271.82 (15.66)	0.004*|0.200
				0.02*	0.01*	0.02*/0.01*		
Left outer macula superior	271.67 (18.19)	277.81 (15.48)	0.16|0.033	277.95 (16.56)	280.38 (14.28)	259.10 (14.96)	272.91 (17.18)	0.006*|0.191
				0.03*	0.01*	0.03*/0.01*		
Right outer macula temporal	290.78 (20.72)	296.25 (17.94)	0.26|0.020	297.00 (20.10)	302.05 (16.90)	278.91 (16.91)	285.18 (14.87)	0.04*|0.138
				0.07	0.01*	0.07*/.01*		
Left outer macula temporal	290.58 (19.87)	294.74 (18.85)	0.40|0.012	297.76 (18.64)	300.14 (18.57)	275.50 (13.09)	283.40 (14.40)	0.001*|0.243
				0.02*	0.006*	0.02*/0.006*		

Right outer macula inferior	262.87 (18.74)	268.47 (18.72)	0.24|0.023	266.10 (17.46)	270.52 (16.17)	256.10 (20.44)	264.55 (23.18)	0.26|0.065
Left outer macula inferior	263.13 (22.72)	267.61 (18.35)	0.39|0.012	265.19 (18.42)	271.30 (17.68)	259.18 (29.92)	260.91 (18.42)	0.38|0.051
Right outer macula nasal	254.38 (17.01)	261.38 (13.89)	0.08|0.050	258.50 (17.19)	263.19 (12.02)	245.22 (13.20)	257.91 (17.00)	0.04*|0.138
					0.04*	0.04*		
Left outer macula nasal	252.52 (17.71)	261.81 (13.72)	0.02*|0.082	258.40 (16.48)	262.38 (12.92)	241.82 (15.16)	260.60 (15.96)	0.004*|0.202
				0.04*	0.007*	0.04*/0.007*/0.05	0.05	
Right GCL-IPL average	77.37 (8.51)	78.90 (11.26)	0.55|0.006	79.30 (9.33)	81.42 (11.01)	73.50 (4.97)	74.55 (10.79)	0.11|0.101
Left GCL-IPL average	74.79 (12.18)	78.50 (8.85)	0.19|0.031	78.18 (12.85)	81.16 (7.29)	69.55 (9.30)	73.91 (9.75)	0.02*|0.164
Right GCL-IPL minimum	71.63 (14.50)	75.00 (16.36)	0.40|0.012	73.70 (16.44)	78.00 (15.23)	67.50 (8.87)	69.82 (17.63)	0.29|0.064
Left GCL-IPL minimum	68.50 (22.62)	75.30 (12.08)	0.16|0.036	75.53 (15.18)	78.79 (7.16)	57.64 (28.27)	69.27 (16.37)	0.01*|0.184
					02*	0.02*		
Right cup-to-disc ratio	0.55 (0.16)	0.41 (0.21)	0.004*|0.129	0.54 (0.19)	0.42 (0.23)	0.59 (0.10)	0.39 (0.18)	0.03*|0.137
Left cup-to-disc ratio	0.54 (0.17)	0.39 (0.19)	0.002*|0.148	0.52 (0.20)	0.39 (0.22)	0.58 (0.11)	0.39 (0.13)	0.02*|0.156
Right cup volume	0.25 (0.21)	0.14 (0.17)	0.02*|0.085	0.25 (0.22)	0.16 (0.19)	0.26 (0.19)	0.09 (0.10)	0.10|0.100
Left cup volume	0.24 (0.23)	0.11 (0.15)	0.07|0.110	0.23 (0.25)	0.13 (0.17)	0.25 (0.21)	0.07 (0.06)	0.07|0.11

RNFL, retinal nerve fiber layer; CSF, central subfield; GCL-IPL, ganglion cell layer and inner plexiform layer.
* indicates a statistically significant result.

result from variation in antipsychotic medication dosages across countries (e.g. Spain, Turkey, Malaysia, UK, USA). In our study, for example, the mean CPZ equivalent dose (even when including high dose outliers) was 35% lower than that reported by (Ascaso *et al.* 2015). The effect of retinal dopamine blockade on atrophy of post-synaptic retinal cells, as described in the Introduction, is an issue in need of further exploration.

A novel and potentially important finding from this study was that the cup-to-disc ratio was enlarged in people with schizophrenia, in both eyes, and independent of diabetes or hypertension. Findings of the enlarged cup-to-disc ratio are typically attributed either to RNFL thinning, vascular compromise (e.g. loss of retinal capillaries) (Geyman *et al.* 2017), or enlarged optic nerves. Because we did not observe evidence of RNFL thinning in schizophrenia, we consider it unlikely that this is involved. On the other hand, the second possibility is supported by prior evidence of vascular abnormalities in schizophrenia (Curtis *et al.* 1999; Moises *et al.* 2015; Najjar *et al.* 2017), including in the retina (Meier *et al.* 2013). To our knowledge, there are no published data on optic nerve size in schizophrenia, and thus it is not clear how robust this finding is, or what might cause this effect. One possibility is inflammation. Ascaso *et al.* (2015) suggested that inflammation in recently psychotic patients may have masked retinal layer degeneration, leading to relatively normal OCT values, in contrast to patients who did not have a recent psychotic episode. In this view, both the relatively normal thickness values we observed and the enlarged optic cup volume and cup-to-disc ratio values, could be due to inflammation. However, several points argue against this. One is that very few of the patients in this study would have met criteria for Ascaso *et al.*'s recent illness episode group, in that their most recent hospitalization was longer than 6 months prior to study participation. Second, evidence of optic nerve edema was not observed upon ophthalmologic examination, which every subject received. Additional studies are needed, therefore, to determine the pathophysiology of cup-to-disc ratio and cup changes in schizophrenia. An enlarged cup-to-disc ratio has previously been observed in MS (see above) and in AD (see above). Therefore, if replicated, this finding in schizophrenia would suggest a shared aspect of pathophysiology with these other neuropsychiatric disorders, and one that may be independent of RNFL and macula thinning (Saidha *et al.* 2011). And, even though the finding is not diagnostically specific, it, and perhaps the variable of cup volume could be useful in tracking disease progression, especially (given the correlation with PANSS Cognitive factor score) regarding cognitive symptoms. An important caveat here is that cup volume, but not a cup-to-disc ratio, was positively correlated with CPZ equivalent medication dose. Whether this reflects a true medication effect, or an illness severity effect, or some other effect is currently unknown. It is possible, however, that the dual correlations of cup volume with PANSS cognitive symptoms and medication dose reflect all three features representing aspects of poor outcome patients. For example, several studies indicate that disorganization (one of the symptoms on the PANSS Cognitive factor) is highly heritable and linked to features such as impaired attention, poor premorbid social adjustment, and poor long-term functional outcome. Moreover, these features typically correlate with each other and have been hypothesized to represent a 'poor outcome' or 'process' subtype of schizophrenia with a strong genetic influence (Farmer *et al.* 1983; Sham *et al.* 1996; Wickham *et al.* 2001; Wickham *et al.* 2002). It may be, therefore, that patients judged to be more severely ill are prescribed higher doses of medication, and

Table 3. Comparisons between subjects medically affected by diabetes and/or hypertension and unaffected subjects (collapsed across schizophrenia and control). Column 4 displays the p values and effect sizes for these between-group comparisons

	Medically unaffected	Diabetes/ hypertension	$p\|\eta_p^2$
Right RNFL	89.83 (18.11)	85.59 (11.81)	0.033|0.016
Left RNFL	90.45 (11.61)	84.45 (10.62)	0.048*|0.062
Right superior RNFL	109.60 (24.04)	104.00 (14.36)	0.32|0.016
Left superior RNFL	114.45 (17.09)	107.68 (16.06)	0.13|0.037
Right inferior RNFL	120.40 (18.13)	112.91 (26.54)	0.19|0.028
Left inferior RNFL	119.10 (19.65)	111.14 (21.07)	0.14|0.035
Right temporal RNFL	61.38 (10.26)	58.09 (8.99)	0.21|0.025
Left temporal RNFL	59.69 (10.03)	55.50 (9.45)	0.11|0.041
Right nasal RNFL	74.00 (13.64)	67.18 (13.03)	0.06|0.057
Left nasal RNFL	67.12 (13.69)	63.50 (15.15)	0.34|0.015
RNFL symmetry	84.48 (15.09)	83.86 (9.70)	0.86|0.000
Right macula CSF	254.71 (26.37)	237.77 (24.53)	0.02*|0.091
Left macula CSF	255.86 (25.56)	239.09 (29.13)	0.02*|0.083
Right macula volume	10.11 (0.57)	9.49 (0.90)	0.001*|0.155
Left macula volume	10.04 (0.60)	9.34 (0.84)	<0.001|0.193
Right macula average	280.67 (15.89)	263.45 (24.97)	0.001*|0.154
Left macula average	278.88 (16.77)	259.45 (23.32)	<0.001*|0.192
Right outer macula superior	280.00 (14.20)	266.55 (15.98)	0.001*|0.161
Left outer macula superior	279.20 (15.29)	266.33 (17.27)	0.004*|0.130
Right outer macula temporal	299.52 (18.52)	282.05 (15.87)	<0.001|0.186
Left outer macula temporal	298.95 (18.42)	279.45 (13.99)	<0.001*|0.226
Right outer macula inferior	268.31 (16.77)	260.52 (21.80)	0.12|0.039
Left outer macula inferior	268.17 (18.10)	260.05 (24.26)	0.14|0.036
Right outer macula nasal	260.90 (14.77)	252.20 (16.35)	0.04*|0.069
Left outer macula nasal	260.44 (14.71)	250.76 (17.94)	0.03*|0.079
Right GCL-IPL average	80.33 (10.10)	74.05 (8.35)	0.02*|0.093
Left GCL-IPL average	79.75 (10.25)	71.73 (9.56)	0.004*|0.136
Right GCL-IPL minimum	75.79 (15.81)	68.71 (13.86)	0.09|0.049
Left GCL-IPL minimum	77.25 (11.58)	63.45 (23.32)	0.004*|0.139
Right cup-to-disc ratio	0.48 (0.22)	0.49 (0.17)	0.84|0.001
Left cup-to-disc ratio	0.46 (0.22)	0.48 (0.15)	0.67|0.003
Right cup volume	0.21 (0.21)	0.18 (0.17)	0.54|0.006
Left cup volume	0.18 (0.22)	0.16 (0.18)	0.66|0.003

RNFL, retinal nerve fiber layer; CSF, central subfield; GCL-IPL, ganglion cell layer and inner plexiform layer.
* indicates a statistically significant result.

that this accounts for our findings. Related to this, some types of antipsychotic and antidepressant medications commonly given to people with schizophrenia act as serotonin agonists (e.g. ziprasidone, selective serotonin reuptake inhibitors) and this can raise intra-ocular pressure and lead to glaucoma, which could contribute to changes in optic nerve parameters (Souza *et al.* 2008) even prior to criteria for glaucoma being met.

This study had several limitations. One is that the sample sizes (32 per group) were relatively small, and the sizes of the subgroups (21 and 11 within each group of 32) were such that some of the tests were likely underpowered. On the other hand, our sample sizes for the two primary groups were similar to, and in some cases larger than, those of several other studies in which between-group differences were reported, and so, at least in most cases, adequate power should have existed to detect effects. Another limitation is that the subgroup with both schizophrenia and diabetes/hypertension was older than the other three subgroups. While this group differed from other groups primarily on macula indices, and these findings could be due to age effects, the inequality in ages precluded our ruling out age as a factor. Because of this, we cannot make any statement about a possible interaction between schizophrenia and medical comorbidity. On the other hand, the lack of a difference between the two primary groups indicated clearly that schizophrenia *alone* did not lead to retinal thinning. A third limitation is that we did not quantify recent or general nicotine intake. The thickness of retinal layers is inversely associated with smoking (Patel *et al.* 2016), although in medically healthy individuals who smoke thinning is not observed (Duman *et al.* 2017), suggesting there may not be a direct or causal relationship. Still, the contribution of smoking, even if indirect, cannot be ruled out in our findings, which is relevant given that people with schizophrenia smoke at a higher rate than the general population. On the other hand, the fact that we did not observe between-group differences on most variables should inspire confidence that at least most of our findings are not secondary to schizophrenia-related smoking rates. However, it is possible that the differences in findings between our study and most other studies are due to differences in smoking rates among schizophrenia patients and other people in other countries. An additional limitation of this and prior OCT studies in schizophrenia is that only a few retinal layers were imaged. While the RNFL and macula have been the most common foci of OCT studies, advances in OCT technology are now making it possible to determine the thickness of individual layers anterior to the GCL-IPL, including the photoreceptor layer. Therefore, much remains to be explored regarding retinal structural impairment in schizophrenia.

Finally, an unanswered question in OCT research, including in schizophrenia, is the origin of the retinal pathology. In one view, retinal thinning parallels cortical thinning, with both being aspects of CNS neuronal degeneration. A second view noted above is that antipsychotic medication can directly cause retinal thinning. An alternative hypothesis, however, is that retinal thinning is secondary to progressive tissue loss in the visual cortex, with this leading to retrograde trans-synaptic degeneration (RTSD). RTSD has been observed experimentally in animal TBI studies, and clinically and histologically in humans [reviewed in (Dinkin, 2017)]. In these cases, occipital lobe injury appeared to lead to the death of cells providing input to the injured cortical regions [i.e. cells in the lateral geniculate nucleus (LGN) of the thalamus], and this, in turn, led to a reduction in retinal ganglion cells, which synapse at the LGN. It is not known at this point

whether retinal atrophy via RTSD occurs secondary to *progressive* occipital tissue loss, as has been observed in schizophrenia, and attributed to increased medication use (Ho *et al.* 2011; Fusar-Poli *et al.* 2013) and other developmental or illness effects (Dorph-Petersen *et al.* 2007; Mitelman & Buchsbaum, 2007; Onitsuka *et al.* 2007; Tohid *et al.* 2015). However, determining the relationships between occipital atrophy and retinal thinning cross-sectionally and longitudinally in schizophrenia would be informative. If such a relationship is observed, and if occipital atrophy preceded evidence of retinal thinning, this would suggest an alternative hypothesis for why our data, and the data of (Chu *et al.* 2012) differed from all other published studies. While preliminary evidence against this hypothesis comes from post-mortem studies indicating normal LGN volumes in schizophrenia (Selemon & Begovic, 2007; Dorph-Petersen *et al.* 2009), both of these studies were small (patient sample sizes of 9 and 15, respectively). Relatedly, occipital lobe atrophy (and subsequent retinal atrophy), would only be expected in the subgroup of patients with the most severe illness course (Mitelman & Buchsbaum, 2007; Onitsuka *et al.* 2007; Tohid *et al.* 2015), and so the two prior studies of LGN volumes may not have had enough power to detect subgroup effects, or between-group differences. On the other hand, RTSD is thought to occur in MS and to be responsible for a proportion of retinal cell loss in this condition (Petzold, 2015; Petracca *et al.* 2017). Since MS often has progressive features, and shares many of the same cognitive impairments found in schizophrenia (Guimaraes & Sa, 2012), we believe that RTSD as one of the causes of retinal changes in at least some schizophrenia patients should be investigated further.

In summary, in a sample of schizophrenia patients that were carefully screened for retinal pathology, and for medical comorbidity that can affect the retina, we did not observe RNFL or macula thinning, which had been reported in several prior studies. In contrast, RNFL, macula, and GCL-IPL thinning were related to the presence of diabetes or hypertension. However, we observed an enlarged cup-to-disk ratio, along with enlarged cup volume, in schizophrenia, and this was observed in both eyes, associated with cognitive symptoms, and unrelated to medical comorbidity.

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Notes

[1] The Cognitive factor consists of the items: poor attention, mannerisms and posturing, conceptual disorganization, difficulty in abstract thinking, and disorientation.

[2] Available from: http://www.retinalphysician.com/articleviewer.aspx?articleID=104438

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