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# Retinal layer abnormalities and their association with clinical and brain measures in psychotic disorders: A preliminary study

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ABSTRACT

Studies utilizing optical coherence tomography (OCT) in psychosis have identified abnormalities in retinal cytoarchitecture. We aim to analyze retinal layer topography in psychosis and its correlation with clinical and imaging parameters. Macular retinal images were obtained via OCT in psychosis probands ($n$ = 25) and healthy controls (HC, $n$ = 15). Clinical, cognitive and structural MRI data were collected from participants. No thinning was noted for the retinal nerve fiber, ganglion cell or inner plexiform layers. We found significant thinning in the right inner temporal, right central, and left inner superior quadrants of the outer nuclear layer (ONL) in probands compared to HC. Thickening of the outer plexiform layer (OPL) was observed in the right inner temporal, left inner superior, and left inner temporal quadrants. The right inner temporal and left inner superior quadrants of both the OPL and ONL showed significant inverse correlations. Retinal pigment epithelium thinning correlated with worse mania symptoms, and thinning in the ONL was associated with worse cognitive function. ONL thinning was also associated with smaller total brain and white matter volume. Our findings suggest that outer retinal layers may provide additional insights into the pathophysiology of psychosis, possibly reflecting synaptic or inflammatory aberrations that lead to retinal pathologies.

## 1. Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are serious mental illnesses characterized by psychotic symptoms as well as cognitive, social and functional deficits. While their pathophysiology is not entirely understood, SZ and BD share various pathophysiologic deficits as evidenced by neuroimaging studies observing reductions in gray and white matter, glial cell dysfunction, and increased inflammatory markers (DeLisi et al., 2006; Kempton et al., 2008; Moorhead et al., 2007; Najjar et al., 2013). There is a growing interest in the study of visual deficits in psychiatry, with visual system aberrations helping to elucidate the underlying neurobiology of psychosis. Studies examining visual disturbances in psychosis have identified deficits in perceptual organization, motion processing, target discrimination, and contrast (Chen, 2011; Chkonia et al., 2012; O'Bryan et al., 2014; Silverstein and Keane, 2011). In addition, electroretinography (ERG) studies, which report retinal potentials after stimulation, have demonstrated a-wave deficits in acute schizophrenia and bipolar disorder, reflecting photoreceptor dysfunction (Balogh et al., 2008; Hébert et al., 2019, 2015).The retina is considered to be a “window into the brain (Chu et al., 2012)”, as the two share embryological origins. Visualization of the retina has been primarily studied using optical coherence

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tomography (OCT), a fast and non-invasive imaging technique that can identify retinal cytoarchitecture (Huang et al., 1991). Changes in retinal structure have been studied in various neurologic disorders, such as Alzheimer's disease, multiple sclerosis, Parkinson's disease, and stroke (Chan et al., 2018; Inzelberg et al., 2004; Osiac et al., 2014; Petzold et al., 2017). Several studies have reported atrophy in the retinal nerve fiber layer (RNFL; Celik et al., 2016; Kalenderoglu et al., 2016; Lee et al., 2013; Mehraban et al., 2016) as well as thinning in the ganglion cell layer and inner plexiform layer complex (GCL-IPL) in SZ and/or BD (Celik et al., 2016; Polo et al., 2018). In a recently published meta-analysis, we demonstrated that RNFL and GCL-IPL complex thinning was consistent across twelve retinal OCT studies in SZ and BD. However, group differences in other retinal regions, such as the choroid, were inconsistent and small in number, and data on the outermost retinal layers was not available (Lizano et al., 2019a).

In our meta-analysis we did not identify a confounding effect of age, sex, or OCT device on retinal layer measures, suggesting that this may be a reliable method for assessing retinal cytoarchitecture in patients with psychosis. Due to small sample size, antipsychotic dosage and smoking status were not meta-analyzed. Two studies analyzing the effects of smoking on retinal layer thickness found no significant associations (Mehraban et al., 2016; Silverstein et al., 2018). Effects of illness duration on retinal thickness are mixed, with an almost equal number of studies reporting significant negative correlations (Chu et al., 2012; Kalenderoglu et al., 2016; Lee et al., 2013; Mehraban et al., 2016; Polo et al., 2018) or no association at all (Ascaso et al., 2015; Celik et al., 2016; Garcia-Martin et al., 2018; Khalil et al., 2017; Silverstein et al., 2018; Topcu-Yilmaz et al., 2018). Kalenderoglu et al. (2016) reported a significant correlation between RNFL thinning and symptom severity. In addition, Silverstein et al. (2018) demonstrated that metabolic disorders such as diabetes and hypertension are correlated with RNFL thinning in SZ. This association has not been widely analyzed in psychosis, but RNFL thinning in patients with metabolic disorders suggests that it may be an important moderator of retinal layer thickness in SZ and/or BD (Zarei et al., 2017).

To our knowledge, no studies have explored cortical or cognitive relationships with retinal measures in patients with psychosis. However, these associations have been investigated in other neurologic disorders and in healthy populations. In multiple sclerosis, peripapillary RNFL and GCL-IPL measures have been positively correlated with gray-matter volume in participants with and without optic neuritis (Saidha et al., 2013). A study by den Haan et al. (2018) in early onset Alzheimer's disease identified an association between total macular thickness and an MRI visual rating score of global and parietal atrophy, which was similarly observed in age-matched healthy controls. A prospective population-based study by Mutlu et al. (2017) observed that thinner RNFL, GCL, and IPL were associated with smaller gray-matter and white-matter volume. In dementia, cognitive decline has been associated with total macular atrophy and RNFL-GCL-IPL complex atrophy (Ito et al., 2019). Ko et al. (2018) showed that in a large prospective, multicenter community-based study of healthy people that thinning of the RNFL was associated with worse cognitive performance at baseline and that being in the lower two quartiles was associated with worse follow up cognitive testing. These studies suggest the presence of retinal-cortical and retinal-cognitive relationships that are stronger in neurodegenerative diseases and that can also be independent of neuropathological processes.

The goal of our study was to identify layer differences within the entire retina in patients with SZ and BD with psychosis compared to healthy controls (HC). We used spectral domain OCT (SD-OCT) to obtain segmentation data on the outer layers of the retina that have previously been difficult to analyze. We assessed the effects of potential confounding factors, such as age, gender, body mass index (BMI), blood pressure, visual acuity, as well as cardiometabolic, smoking and antipsychotic statuses. In addition, we aimed to determine the relationships between retinal structures and symptoms, cognition, and global brain structural measures. We hypothesize that there would not only be thinning of the RNFL, GCL, and IPL layers but also structural alterations in deeper layers of the retina. We also hypothesize that RNFL, GCL and IPL atrophy would be associated with symptom severity, poorer functioning, and worse cognition.

## 2. Methods and materials

### 2.1. Participants

Participants from the Bipolar and Schizophrenia Network on Intermediate Phenotype-2 (B-SNIP2) study were recruited for this preliminary study from the Boston site at Beth Israel Deaconess Medical Center. The study was approved by the Beth Israel Deaconess Medical Center institutional review board and was undertaken out in accordance to The Code of Ethics of the World Medical Association (Declaration of Helsinki). Participants were proficient in English and able to give written informed consent. Probands carried a diagnoses of schizophrenia, schizoaffective disorder or bipolar disorder I with a history of psychosis based on Diagnostic and Statistical Manual of Mental disorders IV (DSM-IV; American Psychiatric Association, 2000) and consensus diagnosis. Fifteen healthy controls and twenty-five patients with psychosis participated in the study: 12 with schizophrenia, 8 with schizoaffective disorder, and 5 with bipolar disorder I with a history of psychosis. We have previously demonstrated there is more overlap than not when it comes to comparing structural, functional, neurophysiological, cognitive and clinical measures between schizophrenia, schizoaffective disorder, and BD with psychosis (Tamminga et al., 2014). Thus, we combined our psychosis patients into one group. General exclusion criteria included a history of (1) substance dependence or abuse within the past 6 months, (2) glaucoma, macular degeneration, retinal occlusions, ocular trauma or myopia $>4.0$ diopters, (3) current pregnancy/breast feeding, (4) head injury with neurological sequelae, (5) intellectual disability, and (6) history of neurologic disorders. Healthy controls were excluded if they had a personal history of psychotic or major mood disorder (SCID-Non-patient edition), a family history of psychosis, or SZ-spectrum diagnoses and treatment with medications affecting cognition. Clinical and demographic information was collected as part of the interview. Smoking status was measured using the Fagerstrom Test for Nicotine Dependence, specifically whether the participant had smoked within the past 30 days. Cardiometabolic status was based on whether the participant had a cardiovascular or metabolic disorder, which included coronary artery disease, hypertension, diabetes, hyperlipidemia, obesity and other related disorders. In probands, we collected information regarding duration of illness and medication status for either first- or second-generation antipsychotic use. Furthermore, we assessed psychosis and mania symptoms using the Positive and Negative Syndrome Scale (PANSS) and Young Mania Rating Scale (YMRS), respectively (Kay et al., 1987; Young et al., 1978). The Brief Assessment of Cognition in Schizophrenia (BACS) and the Birchwood Social Functioning Scale (SFS) was utilized to evaluate cognition and functioning in all participants (Birchwood et al., 1990; Keefe, 2004). We have previously used BACS to measure cognitive functioning in patients with bipolar disorder with psychosis, as well as with SZ and schizoaffective disorder (Tamminga et al., 2014).

### 2.2. Optical coherence tomography

Visual acuity was measured using Snellen eye chart using the metric notation. Pupil dilation was performed when image capturing was difficult. All participants underwent retinal imaging using the Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) at the Massachusetts Eye and Ear Institute. The Spectralis utilizes a scan rate of 40 kHz, scan depth of 1.8 mm, 7 μm axial resolution (3.5 μm/pixel),

**Table 1**
Clinical and demographics information for the sample.

| | HC ($n$ = 15) | Probands ($n$ = 20 SZ; $n$ = 5 BD) | Test Stat ($\chi^2$=$F$) | $p$-value |
|---|---|---|---|---|
| Age (years) | 39.0 (12.6) | 36.2 (13.2) | 0.45 | 0.51 |
| Sex (Female/Male) | 6/9 | 8/17 | 0.029 | 0.86 |
| Race (AA/CA/OT) | 4/9/1 | 6/13/5 | 1.25 | 0.54 |
| OD Visual Acuity | 0.94 (0.25) | 0.82 (0.27) | 1.66 | 0.21 |
| OS Visual Acuity | 0.93 (0.23) | 0.82 (0.31) | 1.33 | 0.26 |
| BMI | 25.9 (4.2) | 29.3 (6.1) | 3.65 | 0.064~ |
| Systolic Blood Pressure | 117.7 (7.9) | 122.7 (14.9) | 1.29 | 0.26 |
| Diastolic Blood Pressure | 74.5 (8.6) | 74.2 (9.3) | 0.007 | 0.93 |
| Cardiometabolic Disorder (Yes/No) | 5/10 | 9/16 | 0 | 1 |
| Smoking Status (Yes/No) | 0/1 | 5/6 | 0 | 1 |
| Duration of Illness (months) | – | 142.6 (161.6) | – | – |
| Antipsychotic Status (Yes/No) | – | 18/7 | – | – |
| BACS Composite Score | 0.034 (1.1) | −0.75 (0.94) | 5.35 | 0.027* |
| SFS Score | 150.5 (15.2) | 128.9 (21.1) | 10.7 | 0.002** |
| PANSS Total Score | – | 54.5 (14.5) | – | – |
| PANSS Positive Symptoms Score | – | 13.2 (4.6) | – | – |
| PANSS Negative Symptoms Score | – | 13.4 (4.3) | – | – |
| YMRS Score | – | 7.2 (6.2) | – | – |

Note: HC = healthy control; AA = African American; CA = Caucasian; OT = Other; OD = right eye; OS = left eye; BMI = body mass index; BACS = Brief Assessment of Cognition in Schizophrenia; SFS = Birchwood Social Functioning Scale; PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale. Mean, standard deviation and count data provided.
~ for $p < 0.1$;
* for $p < 0.05$;
** for $p < 0.01$.

14 μm lateral resolution. Structural measurements for eight retinal layers including the RNFL, GCL, IPL, inner and outer nuclear layer (INL, ONL), outer plexiform layer (OPL), retinal pigment epithelium (RPE), and total retinal thickness were obtained using the Heidelberg Spectralis built-in software: Heidelberg Eye Explorer, version 1.9.10.0. An experienced investigator (MK) assessed whether the automatic segmentation was properly delineated according to the International Nomenclature for Optical Coherence Tomography Panel (Staurenghi et al., 2014) and manually modified those determined to be improperly delineated. This semi-automated approach, combining automatic segmentation with manual corrections from an experienced rater, significantly increases the reliability of deep retinal layer segmentations (Oberwahrenbrock et al., 2018). A thickness map was generated by utilizing an Early Treatment Diabetic Retinopathy Study (ETDRS) grid centered at the fovea and consisting of nine sectors: a central circle with diameter 1 mm, and two concentric rings of diameter 3 mm and 6 mm, each divided into four quadrants (superior, nasal, inferior and temporal). Thickness values corresponding to each of the nine ETDRS grid sectors were obtained for the full retina and for each retinal layer. Overall retinal layer thickness was calculated by averaging the weighted mean of each of the ETDRS grid sectors of both eyes. Retinal layer data was then winsorized to three standard deviations.

### 2.3. Structural MRI

Structural T1-weighted magnetization prepared rapid gradient echo (MPRAGE) images were gathered using GE Signa HDxt ($n$ = 7) and GE Discovery MR750 ($n$ = 17) 3T scanners. The GE Signa HDxt has an 8-channel coil and the GE MR750 has a 32-channel coil. The structural sequence duration was 5 min and 27 s, with the following parameters: 7 ms repetition time, 3 ms echo time, and a flip angle of 11°. Freesurfer 6.0 was used to pre-process structural images and the images were quality controlled and manually edited (OL, VZ). In our sub-sample of participants with both retinal and neuroimaging data, no participants were removed as a result of scanner in-homogeneity or motion. Participants with more than three standard deviations ($N$ = 3) were winsorized to the third standard deviation. Cortical markers utilized in this exploratory analysis included global brain volume, gray matter (GM) volume and thickness, as well as white mater (WM) volume.

### 2.4. Statistical analysis

All statistical analyses were performed using R statistical software (version 3.5.1). Group differences in demographic variables were analyzed via Chi-square and analysis of variance (ANOVA) tests. We used an ANOVA to test the moderating effect of age, sex, race, BMI, systolic and diastolic blood pressure, mean visual acuity, as well as cardiometabolic disorder, smoking, and antipsychotic status. Significant predictors ($p < 0.05$) in the initial models were used for adjusting retinal layers for this confounding effect. Since some retinal measures were not normally distributed, we used a univariate, non-parametric Kruskal–Wallis model with group as the independent variable and retinal parameters as dependent measures. Effect sizes were calculated using Cohen's d. Partial Spearman correlations were run between OCT data and clinical/cortical measures using age, sex, and race as covariates for clinical measures. For structural brain measures (total brain volume, gray matter volume/thickness, and white matter volume), we additionally pre-adjusted for scanner using the intercept adjustment method. We set our significance level at 0.05 for a 2-sided alternative hypothesis test, and we did not correct for multiple comparisons since this was a preliminary study.

## 3. Results

### 3.1. Demographics

A total of 40 participants were included in this preliminary analysis, comprising of 15 HC and 25 probands (16 SZ and 9 BD). Table 1 shows the demographics data. Diagnostic and HC groups were well matched for age, sex, race, bilateral visual acuity, and cardiometabolic disease status (Table 1). In addition, smoking status and systolic/diastolic blood pressure were not significantly different between probands and HC (Table 1). Probands had significant decreases in BACS composite ($F$ = 5.35, $p$ = 0.027) and SFS scores ($F$ = 10.7, $p$ = 0.002).

### 3.2. Moderator effects

We determined that age, sex, systolic and diastolic blood pressure, smoking status and antipsychotic status had no statistically significant

**Table 2**
Kruskal–Wallis non-parametric analysis of retinal layer group differences for individual and combined eyes.

| | OD | | | | OS | | | | OU | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HC | Proband | Cohen's d | *p*-value | HC | Proband | Cohen's d | p-value | HC | Proband | Cohen's d | *p*-value |
| Total Retina | 304.7 (18.2) | 297.2 (19.7) | −0.40 | 0.49 | 307.0 (15.7) | 303.6 (11.9) | −0.25 | 0.34 | 305.9 (15.6) | 300.4 (14.8) | −0.36 | 0.46 |
| RNFL | 26.3 (2.3) | 25.7 (2.5) | −0.24 | 0.37 | 26.4 (2.0) | 26.1 (2.3) | −0.15 | 0.55 | 26.4 (2.1) | 25.9 (2.3) | −0.20 | 0.49 |
| GCL | 37.2 (4.1) | 36.8 (3.3) | −0.12 | 0.60 | 37.6 (4.2) | 37.4 (2.8) | −0.06 | 0.68 | 37.4 (4.0) | 37.0 (2.9) | −0.10 | 0.64 |
| IPL | 30.1 (3.1) | 29.8 (3.0) | −0.10 | 0.88 | 30.4 (2.8) | 30.5 (2.2) | 0.05 | 0.91 | 32.1 (3.0) | 32.0 (2.4) | −0.04 | 0.88 |
| INL | 32.7 (2.5) | 32.2 (1.9) | −0.21 | 0.71 | 32.1 (3.1) | 32.0 (2.0) | −0.03 | 0.77 | 34.1 (2.9) | 33.8 (1.9) | −0.11 | 0.86 |
| OPL | 29.2 (3.5) | 30.3 (3.8) | 0.31 | 0.55 | 27.9 (2.3) | 30.0 (4.2) | 0.62 | 0.083~ | 27.2 (1.8) | 28.5 (3.0) | 0.51 | 0.26 |
| ONL | 76.3 (7.9) | 71.0 (9.7) | −0.61 | 0.081~ | 77.8 (5.8) | 72.8 (8.6) | −0.68 | 0.035* | 68.6 (5.7) | 64.6 (6.9) | −0.63 | 0.074~ |
| RPE | 15.1 (2.6) | 14.9 (2.7) | −0.09 | 0.26 | 14.6 (1.1) | 14.1 (1.1) | −0.40 | 0.13 | 14.9 (1.8) | 14.5 (1.8) | −0.20 | 0.19 |

**Note:** OD = right eye; OS = left eye; OU = both eyes; HC = healthy control; RNFL = retinal nerve fiber layer; GCL = ganglion cell layer; IPL/OPL = inner/outer plexiform layer; INL/ONL = inner/outer nuclear layer; RPE = retinal pigment epithelium. Mean, standard deviation and effect size provided.
~ for $p < 0.1$;
* for $p < 0.05$.

correlation with any of the retinal layer measurements (Supplementary Table 1). Visual acuity was correlated with all layer thicknesses except for the OPL thickness (Supplementary Table 1). Race significantly impacted RPE thickness ($p = 0.027$), while cardiometabolic disorder status had an impact on the total retinal thickness ($p = 0.027$).

### 3.3. Diagnostic group differences

In the proband group there were bilateral reductions in layer thickness for all of the retinal layers, with the exception of OPL which was increased (Table 2). A trending increase in left eye (OS) OPL thickness was observed ($d = 0.62$, $p = 0.083$). Thinning of the ONL was observed in the eyes of all probands compared to healthy controls, reaching statistical significance for the left ($d = -0.68$, $p = 0.035$) but not right eye (OD; $d = -0.61$, $p = 0.081$). After adjusting for visual acuity, only the effects for the OS OPL between probands and healthy controls held ($d = 0.62$, $p = 0.076$). We further examined the inner and outer quadrants for the ONL and OPL layers. We identified OD ONL reductions in the inner temporal ($d = -0.78$, $p < 0.05$) and central ($d = -0.93$, $p < 0.05$) quadrants, as well as OS ONL thinning in the inner superior ($d = -0.81$, $p < 0.05$) and outer superior ($d = -0.63$, $p < 0.1$) quadrants in probands compared to HC (Fig. 1). As for the OPL, probands had greater OD OPL thickness in the inner temporal ($d = 0.74$, $p < 0.05$) quadrant, as well as thicker OS OPL in the inner superior ($d = 0.77$, $p < 0.05$), outer superior ($d = 0.59$, $p < 0.05$), inner temporal ($d = 0.62$, $p < 0.05$) and outer temporal ($d = 0.58$, $p < 0.1$) (Fig. 1). These significant results for the ONL and OPL quadrant analysis held after adjusting for visual acuity. There were no significant eye by quadrant specific differences for the RNFL, GCL, IPL, INL, or RPE layer between probands and HC.

### 3.4. Clinical correlations

Partial Spearman correlations were assessed between retinal measures and clinical variables, including duration of illness, PANSS positive and negative symptom subscores, Young Mania total score, BACS composite score, and SFS score (Table 3). Thinning of the RPE layer was associated with worse YMRS score ($r = -0.43$, $p = 0.036$), specifically the OD inner inferior quadrant ($r = -0.38$, $p = 0.045$). In the overall sample, reduced ONL thickness was correlated to lower BACS composite scores ($r = 0.48$, $p = 0.003$). The bilateral inner nasal, outer superior, and outer nasal regions drove this finding (OD: $r = 0.32$, $p = 0.048$; $r = 0.44$, $p = 0.006$; $r = 0.37$, $p = 0.021$; OS: $r = 0.40$, $p = 0.012$; $r = 0.34$, $p = 0.039$; $r = 0.38$, $p = 0.019$, respectively). There were some trending effects for other layers with clinical data (Table 3), but no correlations existed between retinal layers and duration of illness. A post hoc analysis of OU ONL thickness with BACS subscores in the overall sample demonstrated ONL atrophy was associated with poorer verbal fluency ($r = 0.47$, $p = 0.003$), verbal memory ($r = 0.37$, $p = 0.026$), digit sequencing ($r = 0.36$, $p = 0.029$), symbol coding ($r = 0.47$, $p = 0.004$) and tower of London ($r = 0.52$, $p = 0.001$) scores (Supplementary Table 2). In probands, SFS and BACS scores were not significantly associated with any retinal layers, and in HC, thicker GCL was associated with better SFS ($r = 0.62$, $p = 0.037$) (Supplementary Table 3).

### 3.5. Cortical correlations

The correlation between retinal layers and global brain measures for total brain volume, GM volume/thickness and WM volume were analyzed using partial Spearman correlations. Thinning of the total retina layer ($r = 0.44$, $p = 0.032$) and ONL ($r = 0.53$, $p = 0.008$) was associated with smaller total brain volume in the overall sample (Table 4). The correlation between total retinal thickness and total brain volume was driven by the OD inner superior and inner inferior regions ($r = 0.42$, $p = 0.034$; $r = 0.40$, $p = 0.020$). For the ONL, the bilateral central, inner temporal, outer superior, and outer temporal quadrants were primarily associated with total brain volume (*OD:* $r = 0.42$, $p = 0.023$; $r = 0.39$, $p = 0.048$; $r = 0.58$, $p = 0.002$; $r = 0.41$, $p = 0.039$; *OS:* $r = 0.44$, $p = 0.023$; $r = 0.41$, $p = 0.037$; $r = 0.45$, $p = 0.022$; $r = 0.42$, $p = 0.031$, respectively). In addition, the OS inner superior and nasal regions demonstrated significant positive associations with total brain volume ($r = 0.41$, $p = 0.037$; $r = 0.52$, $p = 0.006$, respectively). Smaller total white matter volume was associated with reduced ONL thickness ($r = 0.43$, $p = 0.034$), driven by the OD central and outer superior regions ($r = 0.39$, $p = 0.049$; $r = 0.47$, $p = 0.015$, respectively). In a post-hoc analysis, we found that in probands, thinning of the RNFL was associated with smaller total brain volume ($r = 0.61$, $p = 0.03$) and GM volume ($r = 0.66$, $p = 0.016$), while thinning of the INL was associated with smaller total GM volume ($r = 0.57$, $p = 0.04$). No significant relationships were observed between retinal and cortical measures in the HC group.

## 4. Discussion

Visual deficits measured via retinal OCT have been useful in understanding the underlying pathophysiologic mechanisms in SZ and BD. In a demographically matched sample of patients compared to HC, we found that visual acuity had a significant effect on retinal layers while there was little to no effect of demographic variables, BMI, blood pressure, cardiometabolic status, smoking status, or antipsychotic use in our study. While we did not replicate the finding of RNFL, GCL or IPL atrophy in patients with psychosis compared to HC, we did identify significant OD ONL thinning of the inner temporal and central quadrants, OS ONL thinning of the inner superior quadrant, OD OPL thickening of the inner temporal quadrant, and OS OPL thickening of the inner superior and inner temporal quadrants in probands compared to

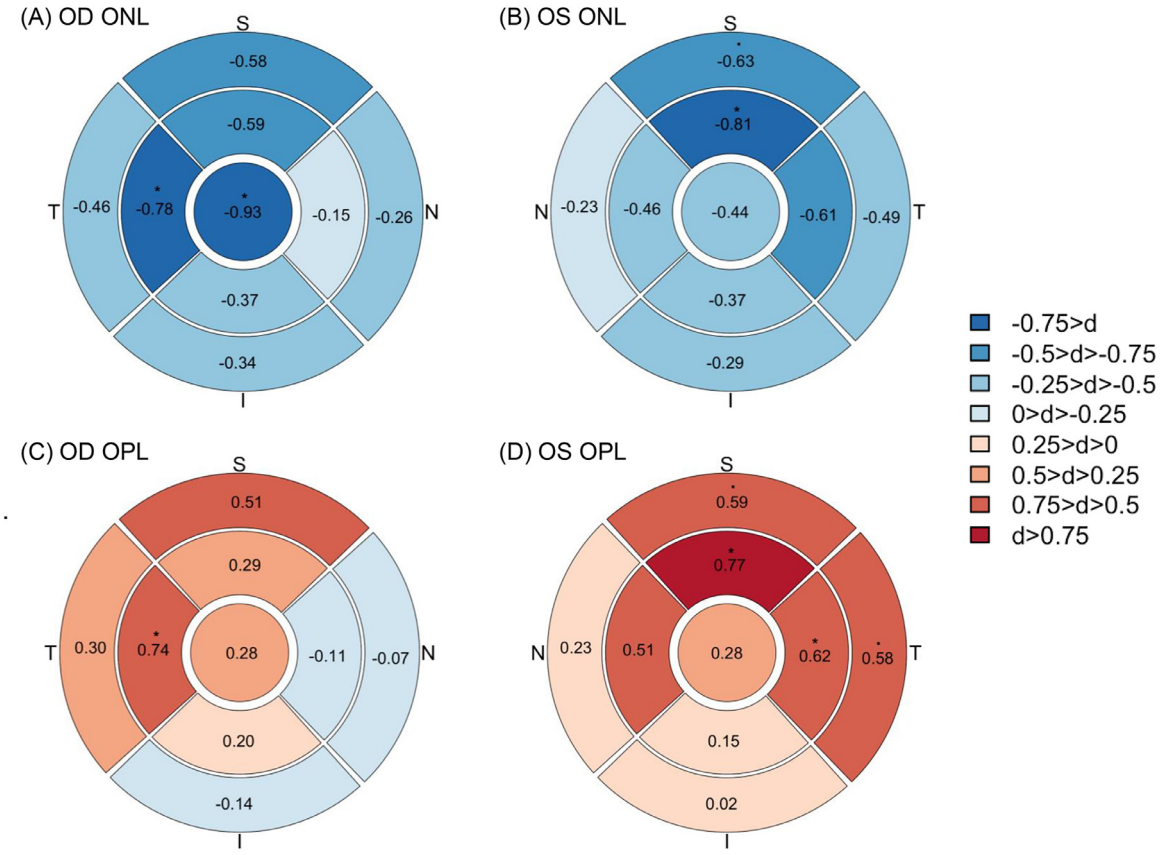


**Fig. 1.** Effect size maps of the inner and outer quadrant for the (A) OD ONL, (B) OS ONL, (C) OD OPL, and (D) OS OPL. Numbers represent Cohen's d values. Color denotes the directionality of the *p*-value, with red being an increased thickness and blue being a decreased thickness. OD = right eye; OS = left eye; ONL = outer nuclear layer; OPL = outer plexiform layer; S = superior; I = inferior; T = temporal; N = nasal. Significance is denoted as, · for $p < 0.10$ and * for $p < 0.05$.

HC. Additionally, we determined that RPE reductions were correlated with worse mania symptoms and that a thinner ONL layer was associated with worse overall cognition. Lastly, we demonstrated that reduced ONL and total retina thicknesses were associated with smaller total brain volume, and that thinner ONL was also correlated with smaller white matter volume. Our findings suggest that the lesser-studied outermost retinal layers may provide additional insights into psychosis pathophysiology.

In contrast to our hypothesis, we did not find reductions in the RNFL, GCL, or IPL in probands compared to HC. While this is not in line with our previous meta-analysis (Lizano et al., 2019a), several studies in SZ and BD have similarly reported a lack of RNFL (Celik et al., 2016; Garcia-Martin et al., 2018; Kalenderoglu et al., 2016; Polo et al., 2018; Silverstein et al., 2018; Topcu-Yilmaz et al., 2018) or GCL-IPL (Khalil et al., 2017; Polo et al., 2018; Silverstein et al., 2018) complex atrophy. These findings may also be influenced by our small and heterogeneous sample size. Another explanation, also hypothesized by Ascaso et al. (2015), could be that psychosis-related inflammation (Aricioglu et al., 2016; Isgren et al., 2017; Lizano et al., 2019a, 2019b, 2018, 2017) may result in alterations of microvascular structure that lead to the disruption and change of retinal cytoarchitecture. In addition, the RNFL, GCL, and IPL did not correlate with symptom severity.

**Table 3**
Partial Spearman correlations between OU retinal layer thickness and clinical measures.

| | PANSS Positive | | PANSS Negative | | YMRS | | Duration of Illness | | SFS | | BACS Composite | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| Total Retina | −0.07 | 0.74 | −0.23 | 0.28 | −0.02 | 0.94 | −0.07 | 0.77 | 0.16 | 0.34 | 0.28 | 0.095˜ |
| RNFL | −0.25 | 0.23 | −0.05 | 0.81 | −0.28 | 0.19 | −0.17 | 0.47 | 0.19 | 0.26 | 0.02 | 0.89 |
| GCL | −0.31 | 0.14 | −0.18 | 0.41 | −0.08 | 0.70 | −0.08 | 0.74 | 0.14 | 0.42 | 0.17 | 0.32 |
| IPL | −0.24 | 0.26 | −0.12 | 0.57 | −0.13 | 0.55 | −0.08 | 0.74 | 0.08 | 0.63 | 0.14 | 0.42 |
| INL | 0.01 | 0.95 | −0.02 | 0.93 | 0.08 | 0.71 | 0.02 | 0.95 | −0.02 | 0.90 | 0.11 | 0.51 |
| OPL | −0.40 | 0.053˜ | −0.10 | 0.65 | −0.29 | 0.17 | −0.23 | 0.33 | −0.20 | 0.24 | −0.31 | 0.064˜ |
| ONL | 0.10 | 0.64 | 0.01 | 0.97 | 0.03 | 0.89 | 0.14 | 0.53 | 0.30 | 0.077˜ | 0.48 | 0.003** |
| RPE | −0.32 | 0.13 | −0.39 | 0.063˜ | −0.43 | 0.036* | −0.25 | 0.27 | 0.26 | 0.13 | 0.17 | 0.31 |

**Note:** OU = both eyes; PANSS = Positive and Negative Symptom Scale; YMRS = Young Mania Rating Scale; SFS = Birchwood Social Functioning Scale; BACS = Brief Assessment of Cognition in Schizophrenia; RNFL = retinal nerve fiber layer; GCL = ganglion cell layer; IPL/OPL = inner/outer plexiform layer; INL/ONL = inner/outer nuclear layer; RPE = retinal pigment epithelium.

˜ for $p < 0.1$;

* for $p < 0.05$;

** for $p < 0.01$. Clinical measures were adjusted for age, sex and race. Retinal measures were not adjusted. SFS and BACS correlations were performed in the whole sample.

**Table 4**
Partial Spearman correlations between OU retinal layer thickness and cortical measures in the overall sample.

| | Whole Brain Volume | | GM Volume | | GM Thickness | | WM Volume | |
|---|---|---|---|---|---|---|---|---|
| | *r* value | *p* value | *r* value | *p* value | r value | *p* value | *r* value | *p* value |
| Total Retina | 0.44 | 0.032* | 0.31 | 0.15 | 0.24 | 0.25 | 0.31 | 0.14 |
| RNFL | 0.31 | 0.14 | 0.28 | 0.19 | 0.19 | 0.36 | 0.15 | 0.49 |
| GCL | 0.18 | 0.41 | 0.14 | 0.52 | 0.24 | 0.26 | 0.11 | 0.62 |
| IPL | 0.11 | 0.62 | 0.06 | 0.79 | 0.19 | 0.37 | 0.06 | 0.79 |
| INL | 0.30 | 0.16 | 0.19 | 0.38 | 0.12 | 0.57 | 0.15 | 0.48 |
| OPL | 0.16 | 0.47 | 0.09 | 0.69 | −0.03 | 0.89 | 0.02 | 0.93 |
| ONL | 0.53 | 0.008** | 0.35 | 0.09~ | 0.30 | 0.16 | 0.43 | 0.034* |
| RPE | 0.05 | 0.82 | −0.08 | 0.73 | 0.02 | 0.92 | −0.13 | 0.55 |

Note: OU = both eyes; GM = gray matter; WM = white matter; RNFL = retinal nerve fiber layer; GCL = ganglion cell layer; IPL/OPL = inner/outer plexiform layer; INL/ONL = inner/outer nuclear layer; RPE = retinal pigment epithelium.
~ for $p < 0.1$;.
* for $p < 0.05$;.
** for $p < 0.01$. Brain measures were adjusted for age, sex, race and scanner sequence. Retinal measures were not adjusted.

Some studies do not report a relationship between the RNFL (Chu et al., 2012; Garcia-Martin et al., 2018; Khalil et al., 2017; Lee et al., 2013; Mehraban et al., 2016; Petzold et al., 2017; Topcu-Yilmaz et al., 2018) and the GCL-IPL (Khalil et al., 2017) complex and disease severity, while others report that thinner RNFL (Kalenderoglu et al., 2016) and GCL-IPL (Celik et al., 2016) thicknesses are associated with worse outcome. We also did not observe relationships between RNFL, GCL, and IPL measures and illness duration, consistent with our meta-analysis (Lizano et al., 2019a). However, the literature for RNFL-illness duration relationships is equally mixed, with some reporting no association (Ascaso et al., 2015; Celik et al., 2016; Garcia-Martin et al., 2018; Khalil et al., 2017; Silverstein et al., 2018; Topcu-Yilmaz et al., 2018) and others reporting positive correlations (Chu et al., 2012; Kalenderoglu et al., 2016; Lee et al., 2013; Mehraban et al., 2016; Polo et al., 2018; Silverstein et al., 2018). For the GCL-IPL complex, Khalil et al. (2017) did not find an association with disease duration, while Garcia-Martin et al. (2018) reported an inverse association. No correlations between cognitive and retinal measures in the overall sample were seen, but the control group demonstrated a positive relationship between BACS composite score and GCL thickness. With regards to cortical measures, we observed a positive correlation between RNFL thickness and whole brain and GM volumes in individuals with psychosis, and this effect was not seen in the overall sample or in HC. This study is the first to integrate retinal-cortical relationships, and our finding suggests that pathophysiologic cortical alterations in psychosis may be reflected in the RNFL. Future studies should examine the role of the RNFL, GCL and IPL in a larger sample of patient with psychosis and integrate measures of the visual-cortical pathway and its structural connectivity. Additionally, a wider venule diameter has been described in SZ using fundus imaging, which is hypothesized to be caused by microvascular dysfunction (Meier et al., 2013). While our sample showed no differences in best-corrected visual acuity between diagnostic groups, other studies in diabetic retinopathy (Durbin et al., 2017) and hypertension (Lee et al., 2019), known to affect retinal microvasculature, showed similar non-findings in BCVA. It would be important to test whether inflammation through microvascular dysfunction affects the thickness of the RNFL, GCL, and IPL, which may explain why no thinning was observed in our study.

To our knowledge, only two studies have analyzed outer retinal layers and supporting regions in psychosis. Starting with the outer nuclear layer, Samani et al. (2018) reported significant reductions in foveal ONL thickness in SZ, and Schönfeldt-Lecuona et al. (2018) reported outer ring ONL reductions in right eye measures. We observed similar, and bilateral, reductions of outer nuclear layer thickness. We correlated ONL thickness alongside those of the RNFL and GCL to test whether its thinning was related to anterograde retinal and found that thinning in the ONL was significantly associated with reductions in the RNFL ($r = 0.39, p = 0.012$) and GCL ($r = 0.33, p = 0.035$). Atrophy in the ONL, which contains rod and cone cells of the retina, may point to a psychosis-related loss of photoreceptor cells that pick up visual information and subsequent downstream loss of visual signal. This is consistent with previous ERG studies in psychosis reporting decreased a-wave (representative of photoreceptor activity) in patients SZ (Balogh et al., 2008; Demmin et al., 2018). Interestingly, Usher syndrome, a major cause of genetic deafness and blindness characterized by congenital sensorineural hearing loss and retinitis pigmentosa, has been associated with a 3–23% risk of SZ (Domanico et al., 2015). Usher syndrome is also associated with brain changes that are similar to those seen in patients with SZ, including cerebral and cerebellar atrophy, hypoplasia of the corpus collosum, and the presence of a septum pellucidum (Domanico et al., 2015). Retinitis pigmentosa is associated with reduced cone densities, thinning of the photoreceptor outer segments and subsequently ONL thinning (Liu et al., 2016). Retinitis pigmentosa is thought to occur due to a ciliopathy (Liu et al., 2016), which has been recently hypothesized as a pathophysiologic mechanism in SZ with DISC1 being the strongest link (Pruski and Lang, 2019). Thus, ONL thinning observed in both SZ and Usher syndrome/retinitis pigmentosa may share similar pathophysiologic mechanisms and lead to the overlap between ophthalmologic and psychiatric disorders.

For the outer plexiform layer, Samani et al. (2018) observed slight increases in thickness, comparable to our results for the OS OPL. Our study did find significant thickening of the bilateral inner temporal OPL and of the OS inner superior quadrants, which may indicate a region-based pathophysiologic mechanism occurring within the OPL. Retinal OCT studies in psychosis vary in how they examine retinal cytoarchitecture, with some studies examining each eye separately (Ascaso et al., 2015; Chu et al., 2012; Kalenderoglu et al., 2016; Khalil et al., 2017; Mehraban et al., 2016; Silverstein et al., 2018, p. 201; Yılmaz et al., 2016), others studying one eye or averaging the values from both eyes (Celik et al., 2016; Garcia-Martin et al., 2018; Lee et al., 2013; Polo et al., 2018; Topcu-Yilmaz et al., 2018). The unilateral results observed in our sample potentially supports the laterality hypothesis in psychosis, which suggests a link between the disorder and aberrant laterality neural or connectivity pathways. Thus, abnormal cerebral lateralization observed in SZ may be reflected as lateralized retinal deficits in the eyes of patients (Okada et al., 2016). For our OPL findings, we further correlated its thickness with that of the RNFL and GCL, but we did not find any significant associations between the two, suggesting that the pathological processes in the OPL may be independently occurring (RNFL: $r < 0.001$, $p = 0.99$; GCL: $r = 0.22$, $p = 0.18$). Studies in Parkinson's disease demonstrate comparable increases in OPL thickness, and infer that foveal remodeling from oxidative stress pathways may explain this finding (Chorostecki et al., 2015; Pilat et al., 2016). Another explanation could be a compensatory synaptic increase, since the OPL is a synaptic layer between photoreceptor, bipolar, and horizontal cells, counteracting the reductions

found in the ONL. In our sample, we found that an increase in OU OPL thickness is significantly associated with reductions in the OU ONL ($r = -0.32$, $p = 0.043$). It is also possible that since the OPL is made up primarily of synapses, it has little resistance to vascular and extracellular changes, thus, the thickening seen within this layer may reflect neuro-inflammatory processes, and the observed ONL thinning may be a result of an expanding OPL (Remington, 2012). This hypothesis is further supported by our findings which showed inverse segmentation results as well as significant correlations for OPL and ONL thickness in the OD inner temporal ($r = -0.49$, $p = 0.001$) and OS inner superior ($r = -0.56$, $p = 0.0002$) quadrants (Fig. 1).

Our study did not find any correlations between ONL or OPL thickness and clinical or functional parameters. Schönfeldt-Lecuona et al. (2018) similarly did not find any correlations for these two regions, but Samani et al. (2018) did report an inverse association between ONL thickness and PANSS negative symptom score. We did find that thicker ONL measures were strongly associated with higher cognitive function in our sample. The ONL demonstrated positive correlations with five of six BACS subscores: verbal fluency, verbal memory, digit sequencing, symbol coding, and Tower of London. This finding suggests that the ONL reflects cognitive function in patients with psychosis. We found that the ONL was the only retinal layer to be significantly correlated with cortical measures, with thinner ONL correlating to reduced total brain and white matter volumes. The ONL may be implicated as a biomarker for the cortical reductions reported in SZ and BD (Hibar et al., 2018; van Erp et al., 2016).

## 5. Limitations

Our study had many strengths, as we were the first study in psychosis to examine the relationship between retinal layer thickness and cognition and brain structure, examine the confounding effects of moderators on retinal layer thickness such as age, smoking and comorbidities, and utilized a weighted mean for analysis of mean eye thicknesses. However, our study had several limitations, including our sample size which is relatively small, such that the group comparisons were underpowered for RNFL differences. We were not able to address the difference in retinal layer changes between our SZ and BD group due to the small size of our sample. Also, a smaller subset of our sample contained MRI structural measures and this did not allow us to examine relationships with visual cortical and thalamic regions. Furthermore, we did not use chlorpromazine equivalents in our correlational analysis, but we did compare the effects of taking vs not taking an antipsychotic medication. Lastly, utilizing swept-source OCT, which allows for higher resolution imaging of retinal layers, may in the future provide more accurate segmentation and measurements of retinal layer thicknesses, especially for the outer retina.

## 6. Conclusion

In summary, we found that OCT-based retinal segmentation of deeper retinal layers was able to inform the pathophysiology of psychosis and disease specific phenotypes. While we do not have direct evidence for OPL thickening and ONL thinning, we hypothesize that synaptic dysfunction and/or inflammatory changes could result in microvascular alterations at the retinal or choroidal levels leading to increases in retinal venule diameter, blood brain barrier disruption, and extracellular swelling. We believe that this same process could be involved in the RNFL, GCL or IPL, which would have limited our ability to detect thinning in these layers in our sample. Additionally, we demonstrated that ONL thickness could be predictive of overall cognitive ability, as well as total brain volume and total white matter volume.

## Disclosures

None of the authors have any financial disclosures or conflicts of interest to report.

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## Supplementary materials

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