Schizophrenia Bulletin vol. 46 no. 1 pp. 43–53, 2020
doi:10.1093/schbul/sbz029
Advance Access publication 21 May 2019

A Meta-analysis of Retinal Cytoarchitectural Abnormalities in Schizophrenia and Bipolar Disorder

Paulo Lizano*[,1,2,4], Deepthi Bannai[1,4], Olivia Lutz[1], Leo A. Kim[3], John Miller[3], and Matcheri Keshavan[1,2]

[1]Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA; [2]Department of Psychiatry, Harvard Medical School, Boston, MA; [3]Retina Service, Massachusetts Eye and Ear, Department of Ophthalmology, Harvard Medical School, Boston, MA

[4]These authors contributed equally to the article.

*To whom correspondence should be addressed; Department of Psychiatry, Beth Israel Deaconess Medical Center, 330 Brookline Ave, KS253, Boston, MA 02215, US; tel: 201-776-6708, fax: 617-667-2808, e-mail: lizanopl@gmail.com

Background: **Schizophrenia (SZ) and bipolar disorder (BD) are characterized by reductions in gray matter and white matter. Limitations in brain imaging have led researchers to use optical coherence tomography (OCT) to explore retinal imaging biomarkers of brain pathology. We examine the retinal layers that may be associated with SZ or BD.** ***Methods:*** **Articles identified using PubMed, Web of Science, Cochrane Database. Twelve studies met inclusion for acutely/chronically ill patients. We used fixed or random effects meta-analysis for probands (SZ and BD), SZ or BD eyes vs healthy control (HC) eyes. We adjusted for sources of bias, cross-validated results, and report standardized mean differences (SMD). Statistical analysis performed using meta package in R.** ***Results:*** **Data from 820 proband eyes (SZ = 541, BD = 279) and 904 HC eyes were suitable for meta-analysis. The peripapillary retinal nerve fiber layer (RNFL) showed significant thinning in SZ and BD eyes compared to HC eyes (*n* = 12, SMD = −0.74, −0.51, −1.06, respectively). RNFL thinning was greatest in the nasal, temporal, and superior regions. The combined peripapillary ganglion cell layer and inner plexiform layer (GCL-IPL) showed significant thinning in SZ and BD eyes compared to HC eyes (*n* = 4, SMD = −0.39, −0.44, −0.28, respectively). No statistically significant differences were identified in other retinal or choroidal regions. Clinical variables were unrelated to the RNFL or GCL-IPL thickness by meta-regression.** ***Conclusion:*** **The observed retinal layer thinning is consistent with the classic gray- and white-matter atrophy observed on neuroimaging in SZ and BD patients. OCT may be a useful biomarker tool in studying the neurobiology of psychosis.**

Key words: schizophrenia/bipolar disorder/optical coherence tomography/retinal nerve fiber layer thickness/ganglion cell layer/choroid thickness/macula volume

Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are major psychiatric disorders that typically present in late-adolescence with pronounced cognitive deficits, functional impairments and psychotic or manic symptoms.[1–3] Despite traditional phenomenological categorization of patients with SZ and BD, these disorders have common neurobiological phenotypes.[4] The neurobiology of SZ and BD are shared and are characterized by reductions in gray matter and white matter as measured by structural neuroimaging.[5,6] However, it is presently difficult to draw firm conclusions about the pathophysiology of SZ or BD using current in vivo structural neuroimaging methods, since existing parcellation techniques cannot identify any of the 6 distinct layers of the neocortex, the latter of which is only accessible via post-mortem neuroanatomical analysis.[7]

Limitations in brain imaging (ie, low image resolution, cost, patient burden) have led researchers to use optical coherence tomography (OCT), a high-resolution, non-invasive retinal imaging tool, to noninvasively identify markers of brain pathology (stroke, Parkinson's disease, Alzheimer's disease, and multiple sclerosis).[8–11] Since the retina and brain develop early from the anterior neural tube, they share many structural and functional similarities, which include similar classes of brain cells (neurons, glial cells), both contain layers, but differ in neuron types (no pyramidal cells in the retina and no photoreceptors in the brain) and by the total number of layers.[12] Additionally, studies in various neuropsychiatric conditions have shown that retinal layer thinning predicts cortical atrophy.[12] When applied to SZ and BD, such biomarkers may have

clinical value and also enhance our pathophysiologic understanding of the disease process. Recent advances in retinal imaging, such as swept-source OCT, have significantly improved on prior methods by enhancing the quantitative assessment of retinal cytoarchitecture.[12] As a result, in addition to the well-studied retinal nerve fiber layer (RNFL), we can now access 10 additional retinal layers.[13] Four of these layers have been systematically analyzed in more than 1 study of patients with SZ or BD: ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), and choroidal layer. A recent meta-analysis showed that the average RNFL thickness was reduced in SZ, but did not include other relevant retinal layers or neurobiologically related groups (such as BD) and was further complicated by methodological limitations (study inclusion and statistical rigor) to their study.[14]

Thus, we performed meta-analyses to investigate which retinal layers show alterations in acutely and chronically ill patients with SZ or BD compared to healthy controls (HCs). Findings from this meta-analysis will identify shared retinal morphological differences across SZ and BD, as well as highlight important gaps in the literature.

Methods and Materials

Search Strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (supplementary table 1),[15] 2 investigators (PL and DB) comprehensively searched studies of retinal layer segmentation in SZ and BP using PubMed, Web of Science, and the Cochrane Collaboration's Database of Systematic Review in July 2018 and again in December 2018. No conference abstracts were included. The primary search strategies were: "schizophrenia OR psychosis OR bipolar disorder" AND "optical coherence tomography OR retinal nerve fiber layer thickness OR macula volume OR ganglion cell layer OR choroidal layer". We also manually evaluated citations within articles to retrieve additional relevant references. The inclusion criteria were: (1) studies assessing OCT in patients with a diagnosis of SZ or BD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition,[16] Diagnostic Interview for Psychosis (DIP)[17] or by a psychiatrist, (2) studies defined as cross-sectional or prospective, (3) necessary data available within the article or upon request, and (4) English language. We excluded articles if there was (1) no control group, (2) no peripapillary RNFL thickness, (3) a significant overlap in study population, or (4) reported data are in a different format from mean and SDs.

Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale and an overall quality score was defined as the frequency of criteria that were met by each study.[18] All studies had Newcastle-Ottawa Scale >6, with a mean score of 6.63. The average agreement from independent raters (PL and DB) was regarded as excellent (intraclass correlation = 0.835, $F = 11.18$, degrees of freedom = 11, $P < .001$).

Data Analysis

The 2 readers independently extracted retinal layer segmentation data that was measured using time domain (TD-OCT), spectral domain (SD-OCT) or swept-source OCT (SS-OCT) technology. Extracted data consisted of mean overall thickness or volume and SD of individual retinal layers; peripapillary RNFL, GCL, IPL, GCL-IPL, GCC (RNFL+GCL+IPL), as well as macular volume (MV), macular thickness (MT), and choroidal thickness (CT) from the eyes of probands (SZ and BD), SZ, BD, or HC participants. The RNFL thickness parameters were also separately evaluated for the inferior, superior, nasal, and temporal regions. None of the included studies reported on outer nuclear layer or outer plexiform layer. Additional collected data included number of eyes, gender, age, level of care, illness stage, disease duration, symptom severity score, medication status, and OCT device/type. Conflicts on inclusion of data were resolved by consensus (between PL and DB) and there was universal agreement on included studies.

The main outcome measure was mean thickness (μm) or volume (mm^3) of one or the mean of both eyes (when provided), to compare the predefined groups. All statistical analyses were performed using the meta package in R (version 3.4.3).[19] Results are reported as Cohen's *d* standardized mean difference (SMD) with 95% confidence intervals (CI) between the proband, SZ or BD eyes compared to HC eyes. We assessed variability within and between studies using the τ^2, χ^2, and I^2 estimate of heterogeneity. We used the inverse variance method, with fixed effects for low heterogeneity across studies ($P > .1$, $I^2 < 50\%$) or random effects ($P < .05$, $I^2 > 50\%$) for studies with greater heterogeneity followed by Hartung-Knapp adjustment.[20,21] To account for publication bias, we visually inspected funnel plots and performed a trim and fill method. Each individual study effect on mean difference was explored by performing a leave-one-out cross-validation. Meta-regression analysis was performed for each retinal layer that consisted of at least 4 studies (RNFL, GCL-IPL, and CT) for categorical and continuous variables.[22] We explored the moderating effect of age, sex, disease duration, symptom severity, device, and NOS scores on RNFL or GCL-IPL thickness. We considered $P < .05$ as significant for the meta-analysis and meta-regression.

Table 1. Meta-analysis Study Characteristics

			Patients			Controls											
Study	Diagnosis	Eyes	*N*	Women (%)	Age (y)	*n*	Women (%)	Age (y)	Diagnostic Criteria	Level of Care	Illness Stage	Disease Duration (y)	Symptom Severity Score	Medication Status	OCT Device	Technique	NOS PL/DB
Ascaso et al[23]	SZ	2	30	23.0%	45.1 (10.4)	30	27.0%	44.5 (10.9)	DSM-IV	IP	Chronic	16.3 (11.2)	PANSS 101.4 (27.7)	Medicated	Stratus (Carl Zeiss)	TD-OCT	7/7
Celik et al[24]	SZ	1	81	20.0%	35.6 (10.1)	41	31.7%	35.5 (15.9)	DSM-IV	OP	Chronic	13.3 (9.2)	PANSS 73.6 (19.8)	Medicated	Spectralis OCT (Heidelberg)	SD-OCT	6/6
Chu et al[25]	SZ	2	49	26.5%	29.9 (8.7)	40	37.5%	29.5 (6.1)	DIP	OP	FEP	4.4 (3.6)	SANS 3.7 (0-16) SAPS 2 (0-10)	Medicated	Stratus OCT3 (Carl Zeiss)	TD-OCT	7/7
Lee et al[26]	SZ	1	30	40.0%	37.2 (10.7)	30	53.3%	35.9 (9.1)	DSM-IV	IP, OP	Acute, Chronic	0-10	NA	Medicated	Cirrus OCT 4000 (Carl Zeiss)	SD-OCT	7/7
Silverstein et al[31]	SZ	2	32	41.0%	40.5 (12.1)	32	44.0%	39.2 (11.0)	DSM-IV	OP	Chronic	NA	NA	Medicated	Cirrus OCT 4000 (Carl Zeiss)	SD-OCT	6/7
Yilmaz et al[28]	SZ	2	34	26.5%	39.9 (10.3)	30	33.3%	38.6 (9.6)	NA	OP	Chronic	NA	NA	NA	Cirrus OCT 4000 (Carl Zeiss)	SD-OCT	6/6
Topcu-Yilmaz et al[27]	SZ	1	59	45.8%	36.6 (9.5)	37	59.5%	32.1 (12.3)	DSM-IV	IP	Acute, Chronic	10.3	PANSS 75.2 (20.1)	Medicated	Spectralis OCT (Heidelberg)	SD-OCT	6/6
Garcia-Martin et al[32]	BD euthymic	1	30	40.0%	49.7 (11.2)	80	46.3%	49.9 (8.8)	DSM-IV	OP	Chronic	16.5 (6.3)	NA	Medicated	Spectralis OCT (Heidelberg)	SD-OCT	6/6
Kalenderoglu et al[33]	BD euthymic	2	43	46.5%	35.6 (10.5)	43	44.2%	40.5 (15.5)	DSM-IV	OP	Chronic	6.8 (10.6)	NA	Medicated	Spectralis OCT (Heidelberg)	SD-OCT	7/7
Khalil et al[29]	BD non-euthymic	1	80	47.5%	30.9 (9.3)	80	42.5%	32.9 (8.7)	DSM-IV	IP	Acute	NA	NA	Medicated	SITA (Carl Zeiss)	SD-OCT	7/7
Mehraban et al[34]	BD non-euthymic	2	30	20.0%	33.8 (9.2)	30	20.0%	31.2 (9.5)	DSM-IV	IP, OP	Acute, Chronic	10.6 (8.6)	NA	NA	3D OCT-1000 (Topcon)	SD-OCT	7/7
Polo et al[30]	BD euthymic	1	23	65.2%	49.7 (8.8)	23	65.2%	49.0 (9.4)	DSM-IV	OP	Chronic	16.1 (6.7)	NA	Medicated	DRI Triton OCT (Topcon)	SS-OCT	7/7

Note: Data are presented as mean (SD). SZ, schizophrenia; BD, bipolar disorder; DSM, Diagnostic and Statistical Manual; DIP, Diagnostic Interview for Psychosis; PANSS, Positive and Negative Symptom Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; IP, inpatient; OP, outpatient; OCT, optical coherence tomography; TD, time domain; SD, spectral domain; SS, swept source; NOS, Newcastle-Ottawa Scale; PL/DB, study authors.

Results

Studies Selection

Supplementary figure 1 illustrates the selection process for the articles included in the meta-analysis. One hundred eighty-two articles were gathered using predefined search terms, and one article was found using other sources. After removing duplicates, 74 papers were screened and 52 studies were excluded. The remaining 22 full-text papers were assessed. Nine studies were excluded due to being solely commentary (n = 2), overlapping with other studies (n = 5), few cases of SZ or BD (n = 1), retinal vascular study (n = 1), and for necessary data not being provided (n = 1). Twelve studies were eligible for quantitative analysis, which included 521 patients (SZ = 315 and BD = 206) and 496 HC (table 1).[23–34]

Differences in Peripapillary RNFL Thickness

Twelve studies were analyzed for overall peripapillary RNFL thickness with a total of 820 eyes from probands (541 SZ and 279 BD) and 904 eyes from HC (575 in SZ and 329 in BD studies). Compared to HC eyes, the overall peripapillary RNFL was thinner in probands (SMD = −0.74, CI = −1.15 to −0.33, P = .002), SZ (SMD = −0.51, CI = −0.85 to −0.17) and BD eyes (SMD = −1.06, CI = −2.11 to 0), see figure 1. Qualitative assessment of the funnel plot was not indicative of a publication bias (supplementary figure 2A). In meta-regression analyses, age, sex, disease duration, OCT device, and NOS score were all unrelated to the RNFL thickness (supplementary table 2). Meta-regression analyses were not performed for psychosis severity, smoking status or antipsychotic dosage due to the small number of studies.

The 12 studies included the nasal and temporal peripapillary RNFL thickness measurements. Significant reductions in the nasal RNFL thickness were observed in probands (SMD = −0.26, CI = −0.36 to −0.17, P < .001), SZ (SMD = −0.28, CI = −0.52 to −0.04), and BD eyes (SMD = −0.25, CI = −0.41 to −0.09) compared to HC eyes (figure 2A) and there was no indication of publication bias (supplementary figure 2B). For the temporal RNFL thickness, there was significant thinning observed in probands (SMD = −0.23, CI = −0.40 to −0.06, P < .001) and SZ eyes (SMD = −0.19, CI = −0.31 to −0.07), but not for BD eyes (SMD = −0.28, CI = −0.67 to 0.10) compared to HC eyes (figure 2B). The effect remained significant in probands after adjusting for publication bias (SMD = −0.20, CI = −0.37 to −0.034, P = .023, supplementary figure 2C).

Seven studies included the superior and inferior peripapillary RNFL thickness, and the sample consisted of 460 patient eyes (320 SZ and 140 BD) and 514 HC eyes (374 in SZ and 140 in BD studies). Significant thinning was observed for the superior RNFL between probands and HC (SMD = −0.41, CI = −0.77 to −0.06, P = .03), and this effect was lost after adjusting for publication bias (SMD = −0.35, CI = −0.70 to 0.001, P = .05) (figure 2C, supplementary figure 2D). No significant superior RNFL thinning was seen in SZ (SMD = −0.34, CI = −0.88 to 0.20) compared to HC eyes, but there was a significant reduction in BD eyes (SMD = −0.59, CI = −0.83 to −0.35). In regards to the inferior RNFL thickness, there was a trending reduction in proband eyes compared to

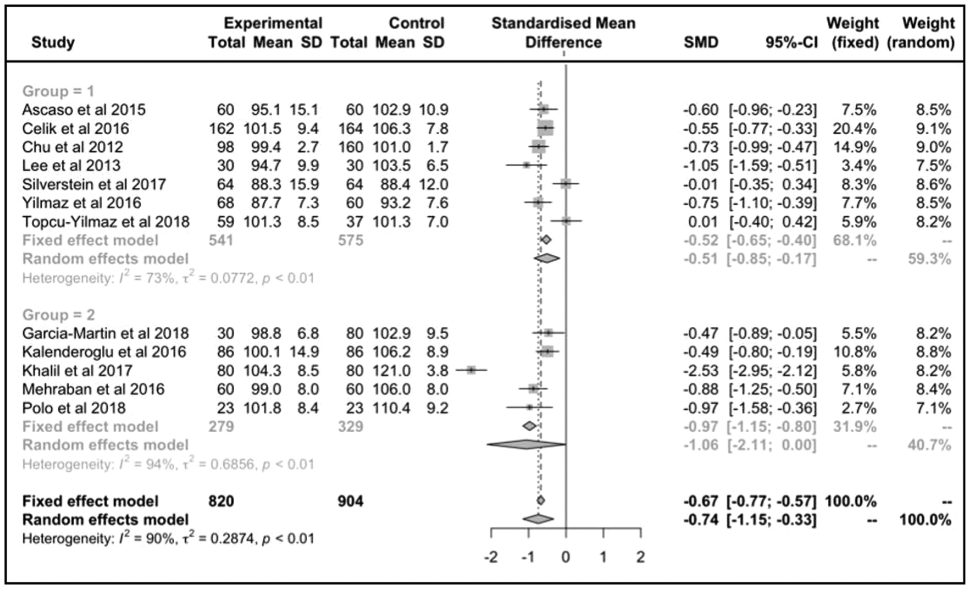

Fig. 1. Meta-analysis of peripapillary RNFL OCT data. Inverse variance with fixed and random effects for RNFL data from SZ eyes (group 1), BD (group 2), or probands compared with HC eyes. Number in the total row includes eyes for which a mean difference could be calculated. Horizontal bars indicate 95% CI. RFNL, retinal nerve fiber layer; SMD, standardized mean difference; OCT, optical coherence tomography; SZ, schizophrenia; BD, bipolar disorder; HC, healthy control.

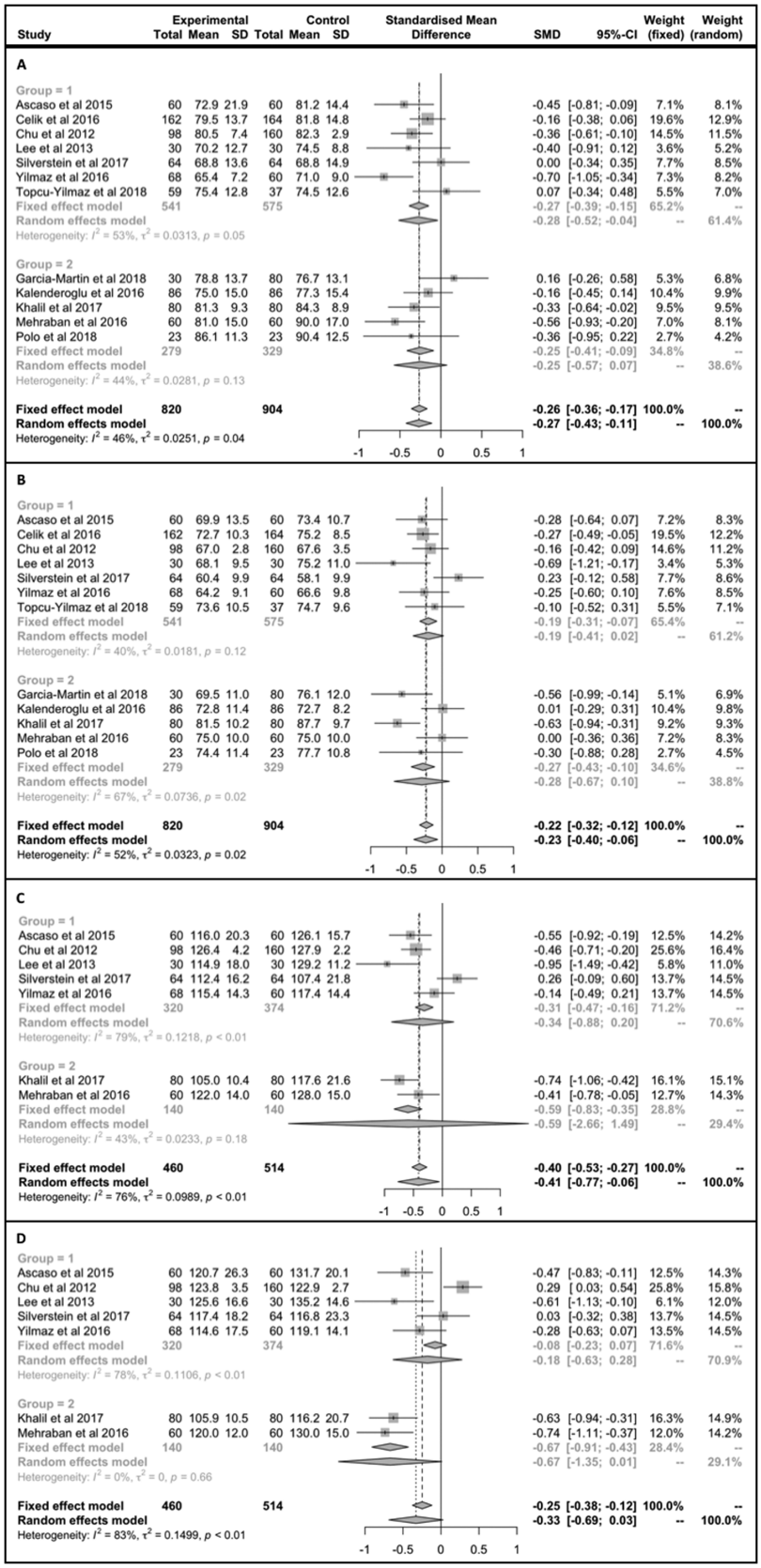

Fig. 2. Meta-analysis of nasal, temporal, superior, and inferior RNFL OCT data. Inverse variance with fixed and random effects for (A) nasal, (B) temporal, (C) superior, and (D) inferior RNFL data from SZ eyes (group 1), BD (group 2) or probands compared with HC eyes. Number in the total row includes eyes for which a mean difference could be calculated. Horizontal bars indicate 95% CI. RFNL, retinal nerve fiber layer; SD, standard deviation, SMD, standardized mean difference; OCT, optical coherence tomography; SZ, schizophrenia; BD, bipolar disorder; HC, healthy control.

HC eyes (SMD = −0.33, CI = −0.69 to 0.03, P = .065), but this result did not hold after publication bias adjustment (SMD = −0.059, CI = −0.45 to 0.33, P = .74) (figure 2D, supplementary figure 2E). Significant inferior RNFL thinning was observed in BD eyes (SMD = −0.67, CI = −0.91 to −0.43), but not in SZ eyes compared to HC eyes.

Differences in GCL-IPL, GCC, and GCL

The peripapillary GCL-IPL was reported in 4 studies, with a total of 329 eyes (226 SZ and 103 BD) and 331 eyes from HC (228 in SZ and 103 in BD studies). Celik et al[24] provided separate GCL and IPL volume measurements that we combined to give a "GCL-IPL" value, and Khalil et al[29] provided the GCC measurement that we separated from the RNFL to give a "GCL-IPL" value. Significant GCL-IPL reduction was seen between probands and HC (SMD = −0.39, CI =−0.55 to −0.24, P < .001), as well as in SZ (SMD = −0.44, CI = −0.63 to −0.26) and in BD (SMD = −0.28, CI = −0.56 to −0.01) (figure 3A). Quantitative analysis via the trim and fill method indicated slight bias, and the results remained significant after adjustment (SMD = −0.44, CI = −0.58 to −0.31, P < .001, supplementary figure 3A). In meta-regression analyses, age, sex, OCT device, and NOS score were all unrelated to GCL-IPL (supplementary table 2). Meta-regression analyses were not performed for disease duration, psychosis severity, smoking status or antipsychotic dosage because of a small number of studies.

Two BD studies reported the GCC thickness, with a total of 103 BD eyes and 103 HC eyes, and there was a significant reduction observed (SMD = −0.94, CI = −1.23 to −0.65, P < .001) (figure 3B). Qualitative assessment of the funnel plot was not indicative of a publication bias (supplementary figure 3B).

Two studies (1 SZ and 1 BD) analyzed GCL volume with a total of 248 eyes (162 SZ and 86 BD) and 250 eyes from HC (164 in SZ and 86 in BD studies). There was no significant reduction of GCL volume in probands (SMD = −1.83, CI = −9.53, 5.88, P = .20) (figure 3C). There was a reduction in GCL volume in SZ and BD separately, but because of high heterogeneity between the 2 studies, there was no significant difference. Qualitative assessment of the funnel plot showed publication bias, but there were not enough samples to perform the trim and fill method (supplementary figure 3C).

Differences in CT

Four studies examined the average CT. The sample consisted of a total of 330 eyes (221 SZ and 109 BD eyes) and 310 eyes from HC (201 in SZ and 109 in BD studies). No significant differences in CT thickness was observed between probands and HC (SMD = −0.01, CI = −0.43 to 0.42, P = .96), SZ (SMD = −0.09, CI = −2.31 to 2.73) or BD eyes (SMD = 0.16, CI = −0.10 to 0.43) (supplementary figure 4a). Qualitative analysis indicated publication bias, and quantitative adjustment indicated no significant difference between patients and controls (SMD = −0.25, CI = −0.71 to 0.20, P = .21, supplementary figure 5a).

Differences in Macula Thickness and Volume

Four studies (3 SZ and 1 BD study) analyzed MT with a total of 185 eyes (162 SZ and 23 BD) and 177 eyes from HC (154 in SZ and 23 in BD studies). No significant reduction of MT was observed (SMD = −0.61, CI = −1.46 to 0.25, P = .11) (supplementary figure 4b), and this remained the case after adjusting for publication bias (SMD = −0.27, CI = −1.05 to 0.50, P = .40, supplementary figure 5b). Four SZ studies assessed MV in a total of 252 SZ eyes and 314 HC eyes. No significant differences in MV were seen (SMD = −0.46, CI = −1.60 to 0.69, P = .29) (supplementary figure 4c). After adjusting for publication bias there was a significant reduction of MV between SZ and HC (SMD = −0.20, CI = −0.37 to −0.03, P = .023, supplementary figure 5c).

Overall, the largest effect sizes between probands and the HC groups were seen for the peripapillary RNFL, superior RNFL, and GCL-IPL (figure 4). The effects sizes were smaller for the nasal and temporal RNFL. The overall and nasal RNFL and GCL-IPL were the only segments that were significantly reduced in all of the group contrasts.

Discussion

Our meta-analysis findings, which were cross-validated and controlled for publication bias, demonstrated: (1) significant thinning in the overall and nasal peripapillary RNFL in patients, SZ, and BD group, (2) significant temporal RNFL thinning in the proband group, while thinning in the superior and inferior RNFL was observed only in the BD group, (3) significant GCL-IPL thinning in the proband, SZ, and BD group, whereas the GCC was significantly thinner in the BD group, and no differences were observed for the GCL measure, (4) significant reduction in MV after adjustment for publication bias, but there is no significant differences for the choroidal or macula thickness, and (5) meta-regression analysis demonstrated that potential confounding variables (age, sex, disease duration, OCT device, and NOS score) were unrelated to the RNFL or GCL-IPL thicknesses. Of note, this meta-analysis spans 3 generations of OCT-device technology and provides a valuable summary of available data on available retinal layers from peripapillary RNFL to CT in patients with SZ and BD. We also show that the findings from this meta-analysis support the concept that SZ and BD are disorders for which OCT may provide useful data on the extent of neurodegenerative pathology.

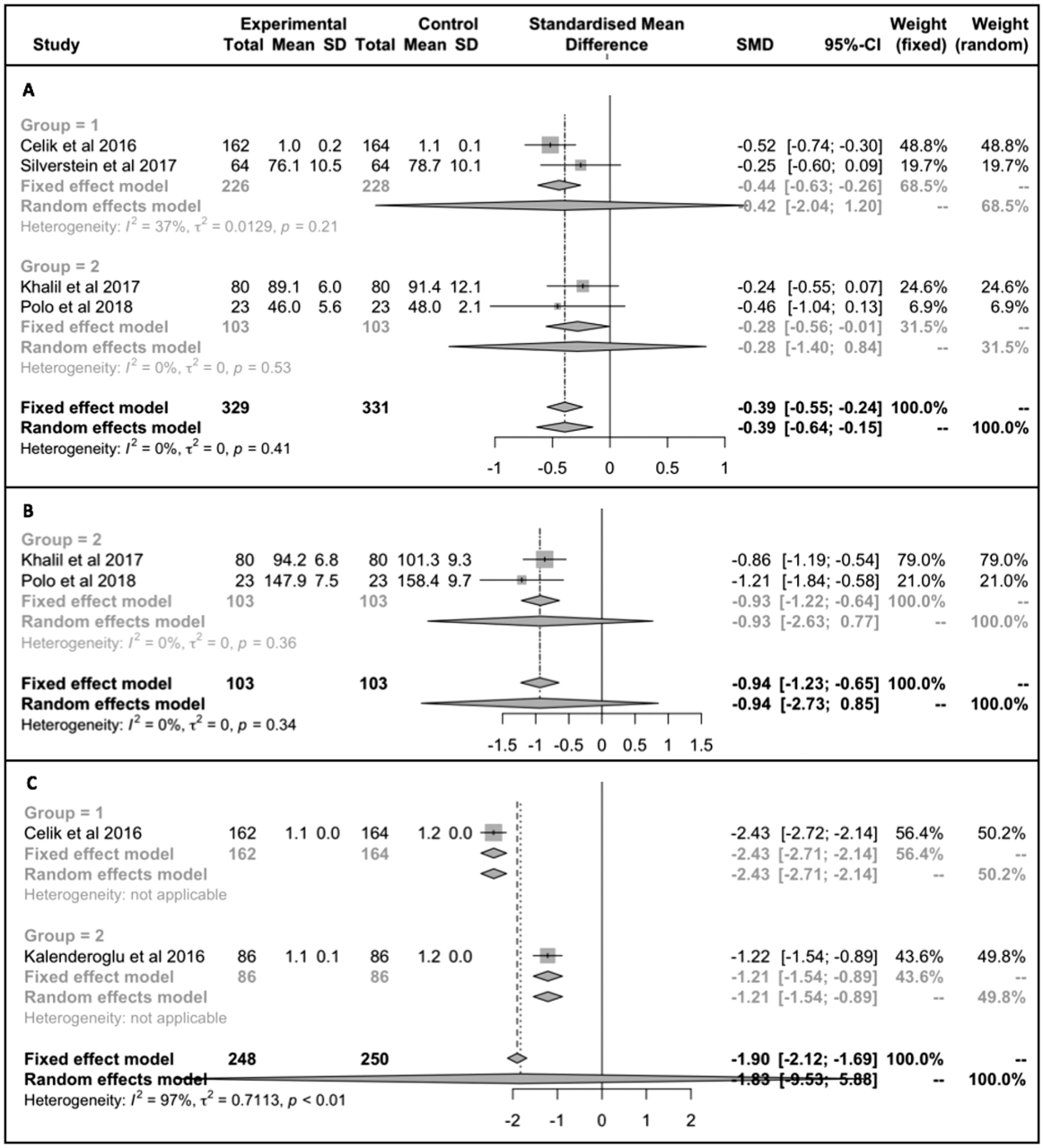

Fig. 3. Meta-analysis of peripapillary GCL-IPL, GCC, GCL OCT data. Inverse variance with fixed and random effects for (A) GCL-IPL, (B) GCC, and (C) GCL data from SZ eyes (group 1), BD (group 2) or probands (when available) compared with HC eyes. Number in the total row includes eyes for which a mean difference could be calculated. Horizontal bars indicate 95% CI. GCL, ganglion cell layer; IPL, inner plexiform layer; GCC; ganglion cell complex; SMD, standardized mean difference; OCT, optical coherence tomography; SZ, schizophrenia; BD, bipolar disorder; HC, healthy control.

RNFL Findings

We examined peripapillary RNFL abnormalities in probands. Most studies have reported on RNFL thickness since the segmentation of this layer is reliable between OCT devices.[11] Structurally, the RNFL and GCL are first-order neurons, with the former consisting of unmyelinated ganglion cell axons that run parallel to the surface of the retina and converge to form the optic nerve, which projects to the lateral geniculate nucleus of the thalamus, providing sensory input to the visual cortex.[35] Axonal damage can occur at any point in this pathway and is hypothesized to give rise to retrograde trans-synaptic axonal degeneration (RTSD), resulting in atrophy of the inner retinal layers, such as the RNFL and GCL-IPL.[35] For example, occipital lobe traumatic brain injury in animal models results in a reduction in the number of cells in the lateral geniculate nucleus of the thalamus, leading to reductions in retinal ganglion cells.[36] It is important

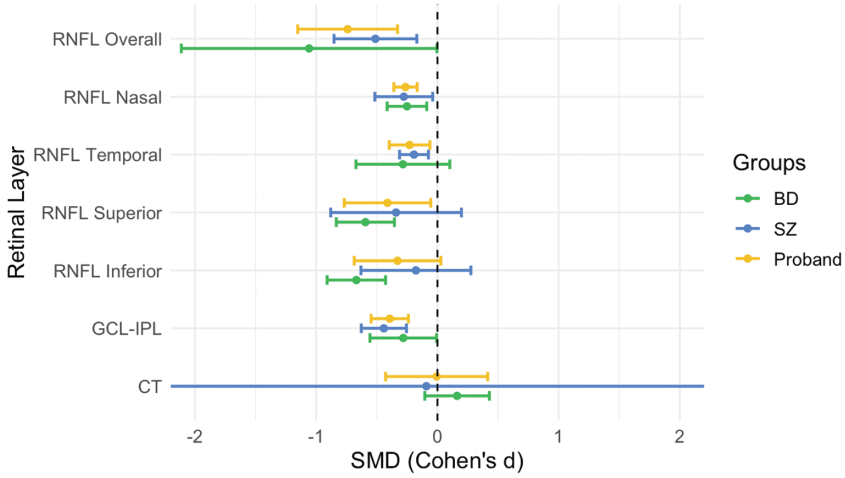

Fig. 4. Mean effect size comparisons of OCT layer segmentations. Circles indicate SMD (Cohen's *d*) effect size and horizontal bars indicate 95% CI. Groups are shown in green (BD), blue (SZ), and yellow (probands) compare to HC eyes. SMD, standardized mean difference; OCT, optical coherence tomography; SZ, schizophrenia; BD, bipolar disorder; HC, healthy control; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell layer; IPL, inner plexiform layer; CT, choroidal thickness. For color, see the figure online.

to note that the thalamus, through its higher order nuclei, is a major relay center with connections to the cerebral cortex, striatum, and cerebellum, which modulate a number of cognitive domains.[37] The thalamus is also one of the brain regions that is most affected in SZ and BD as evidenced by alterations in neuronal number, volume, neurochemistry, functional activation, and structural connectivity.[37–39] Thus, axonal damage caused by aberrations in the microvasculature or in inflammatory and oxidative stress pathways may result in RTSD that can be examined through the eye, but no studies to date have tested this hypothesis in SZ or BD.

According to our meta-analysis, there was significant (though with a moderate effect size) thinning of the peripapillary RNFL for the overall and nasal region in the combined SZ and BD group, and the effect size for the overall RNFL is similar to the strongest single structural brain alteration observed in SZ.[40] One study found significant thinning of the nasal parafoveal RNFL in SZ compared to HC, but not in the overall or temporal region.[41] While our meta-analysis consisted of a mix of acutely and chronically impaired patients recruited from both inpatient and outpatient settings, we did not identify an effect of disease duration on RNFL thickness. We could not perform a meta-regression of acute vs chronic states since many of the studies combined acute and chronic course. However, 5 studies reported a significant negative relationship between RNFL thickness and disease duration,[25,26,30,33,34] while 6 others did not observe a relationship.[23,24,27,29,31,32] Additionally, RNFL thinning was associated with worse clinical symptom severity in one study,[33] no association in 7 studies[24–27,29,32,34] and when stratified by recent illness episode vs non-recent illness episode or by treatment responsive vs refractory, there were no differences in RNFL thickness for the recent illness vs controls or between treatment response groups.[23,24] In order to explain these findings, Ascaso hypothesized that neuro-inflammation, which can occur during acute episodes, may increase RNFL thickness, thus masking thinning in RNFL that are seen in chronic SZ and BD patients.[23]

RNFL thickness was not affected by confounders such as OCT device, age or gender, suggesting that RNFL thickness might be reliably measured with various devices and independent of age and gender. Despite the fact that none of the studies in this meta-analysis independently showed a relationship between RNFL thickness and age, it is important to note, however, that RNFL thins with age and is likely an important confounder. Nine of the 12 studies reported on the exclusion of participants with refractive errors greater than 1.0–6.0 diopters, which is a known confounder for chorioretinal thickness. We were unable to assess the effect of cardiometabolic disease, medications or smoking on RNFL thickness via meta-regression. However, one study showed that the presence of metabolic disorder (diabetes and hypertension) was associated with a significant reduction in RNFL, which might have been confounded by age.[31] Another group demonstrated RNFL thinning in patients with metabolic syndrome.[42] These findings suggest that cardiometabolic disorders, which are overrepresented and undertreated in psychotic disorders, are associated with thinning of retinal structures, and this association has been rarely addressed in past studies; future studies should evaluate the effect of cardiometabolic disorders on retinal layer thickness. One study did not find an association with antipsychotic dosage[31] and another study did not reveal an effect of smoking.[34] More research is needed in investigating the potential confounding effects of medical comorbidities, medication, and smoking on retinal layer thickness.

GCL, GCL-IPL, and GCC Findings

In addition, we examined the role of the GCL-IPL, GCL, and GCC segmentation in patients with SZ and BD. Fewer studies have reported on these layers since previous devices, such as TD-OCT, could not precisely segment these layers due to poor image resolution. However, advances in OCT technology with SD-OCT and SS-OCT now allow for improved segmentation which may have important pathophysiological implications for studying SZ and BD. The GCL rests below the RNFL and is comprised of ganglion cell soma with interspersed astrocytes and displaced amacrine cells. Dendrites from ganglion cells synapse in the IPL with bipolar and amacrine cells, and 80% of ganglion cell processes project to the dorsal lateral geniculate nucleus of the thalamus. Therefore, decreases in GCL and IPL may reflect neuronal atrophy, synaptic loss, or RTSD.

While GCL and IPL measurements are new to studying SZ and BD, previous studies in multiple sclerosis have shown that these layers are better markers of disease severity than the RNFL.[43] This is likely due to the fact that the RNFL is more sensitive to vascular changes associated with gliosis and inflammation,[44] which would impact OCT measurements. One study examined GCL and IPL thickness, but it was excluded from our meta-analysis because of missing mean and SD values; however, in that study significant temporal parafoveal GCL and nasal parafoveal IPL reductions were observed in patients with SZ compared to HC.[41] Additionally, decreased GCL and IPL volumes were greatest in treatment-refractory SZ compared to responsive patients[24] and another study demonstrated reductions in peripapillary and macular GCL-IPL reductions in BD.[30] While our results demonstrating reduction in GCC and GCL-IPL are preliminary, they suggest the involvement of either the GCL and/or the IPL in psychosis pathophysiology; future studies are needed to determine which layer is the most affected.

Our analysis did not reveal any significant relationships between GCL-IPL measures and OCT device, age or sex, and we were not able to examine other clinical variables because of limited data availability. However, Silverstein et al[31] showed that GCL-IPL average thickness was thinner in patients with hypertension or diabetes, but this relationship may be confounded by age, as noted above. Another study showed significant correlations between thinner GCL and IPL volumes and worse disease parameters, such as symptom severity, clinical global impression, and disease duration; in addition, these relationships were stronger for GCL and IPL than those seen with RNFL thickness.[24] Celik et al[24] also showed that GCL-IPL volume was smaller in treatment-refractory patients compared to responsive patients. On the other hand, Garcia-Martin et al,[32] found a strong positive correlation between GCL thickness and disease duration, whereas Khalil et al[29] did not find any associations between GCC and clinical measures of disease severity or duration. No differences were observed for GCL volume between smokers and non-smokers.[33] It is possible that thinning of the GCL-IPL may be related to neuronal loss and/or synaptic pruning, which are prominent pathophysiologic hypotheses in SZ, though further systematic studies are needed.[37,45]

CT Findings

According to our meta-analysis, there were no differences in CT between patients and controls, nor when stratified by diagnostic groups. Structurally, the choroid supplies the outer retinal with nutrients and maintains the temperature and volume of the eye. The choroidal circulation accounts for 85% of total blood flow in the eye, is rapidly affected by systemic influences and can function as a repository for immunoreactive cells.[46] Thus, similar to the RNFL thickness, the lack of significant findings for CT might be due to neuro-inflammatory changes that mask changes. Similar to the observations of GCL-IPL, CT was thinner in refractory vs responsive patients, and CT was negatively related with worse disease severity,[24] whereas another study found a weak negative correlation between disease duration and CT.[27] Since the current literature is mixed, future studies are needed to clarify the role of CT abnormalities in SZ and BD.

Macula Findings

Few studies included either MV or MT, even fewer studies examined sub-regions of the macula, and no studies provided retinal segmentation of the macula. We found a significant reduction in MV after adjusting for publication bias, but none for MT. Few studies have examined the relationship between clinical measures and MV or MT, and no significant correlation was found for disease duration or psychosis symptom severity.[23,25] Forthcoming studies should include retinal segmentation of the macula.

Limitations

There are several limitations associated with this meta-analysis. For example, we pooled studies with relatively small sample sizes stemming from a small number of papers that met our inclusion criteria. There was also variability in the reporting of retinal layers among studies. Thus, data were pooled from the right and left eyes when this information was provided. Additionally, reporting of the GCL-IPL was quite variable, and we pooled the GCL, IPL, and GCL-IPL data to achieve sufficient statistical power for this meta-analysis. Publication bias, study heterogeneity, sample characteristics, and OCT device quality were also limitations, but these were addressed by utilizing random effect models when appropriate,

adjusting for publication bias, performing a cross-validation analysis, and conducting a meta-regression on OCT device type.

Conclusion

In summary, OCT-based retinal layer segmentation has the potential to unravel the pathophysiology of neurodegeneration in psychosis by inspecting this at a structural level. RNFL and GCL-IPL atrophy affects axons and neurons and may reflect early pathophysiologic deficits occurring at the thalamus and/or its projections to the cerebral cortex, striatum, and cerebellum, which we hypothesize can occur via RTSD. Thus, retinal imaging may have clinical value as a non-invasive diagnostic biomarker and also enhance our pathophysiologic understanding of SZ and BD.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Funding

This work was supported in part by Sydney R. Baer Jr Foundation and National Institute of Health Harvard Catalyst grant 1KL2TR002542.

Acknowledgments

We thank Dr. Patricia D'Amore for her collaboration and contribution to this study. None of the authors have any financial disclosures or conflicts of interest to report.

References

1. Insel TR. Rethinking schizophrenia. *Nature*. 2010;468(7321):187–193. doi:10.1038/nature09552
2. Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. Forloni G, ed. *PLoS One*. 2015;10(2):e0116820. doi:10.1371/journal.pone.0116820
3. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 2007;64(5):543–552. doi:10.1001/archpsyc.64.5.543
4. Tamminga CA, Ivleva EI, Keshavan MS, et al. Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *Am J Psychiatry*. 2013;170(11):1263–1274.
5. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry*. 2005;162(12):2233–2245. doi:10.1176/appi.ajp.162.12.2233
6. Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Arch Gen Psychiatry*. 2008;65(9):1017–1032.
7. LaGrow TJ, Moore MG, Prasad JA, Webber A, Davenport MA, Dyer EL. Cytoarchitecture and layer estimation in high-resolution neuroanatomical images. *bioRxiv*. 2018:445742.
8. Wong TY, Klein R, Sharrett AR, et al.; ARIC Investigators. Atherosclerosis Risk in Communities Study. Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA*. 2002;288(1):67–74.
9. Inzelberg R, Ramirez JA, Nisipeanu P, Ophir A. Retinal nerve fiber layer thinning in Parkinson disease. *Vision Res*. 2004;44(24):2793–2797.
10. Danesh-Meyer HV, Birch H, Ku JY, Carroll S, Gamble G. Reduction of optic nerve fibers in patients with Alzheimer disease identified by laser imaging. *Neurology*. 2006;67(10):1852–1854.
11. Petzold A, Balcer LJ, Calabresi PA, et al.; ERN-EYE IMSVISUAL. Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. *Lancet Neurol*. 2017;16(10):797–812.
12. London A, Benhar I, Schwartz M. The retina as a window to the brain-from eye research to CNS disorders. *Nat Rev Neurol*. 2013;9(1):44–53.
13. Cruz-Herranz A, Balk LJ, Oberwahrenbrock T, et al. The APOSTEL recommendations for reporting quantitative optical coherence tomography studies. *Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology*. 2016;86:2303–2309. doi:10.1212/WNL.0000000000002774
14. Pan J, Zhou Y, Xiang Y, Yu J. Retinal nerve fiber layer thickness changes in Schizophrenia: a meta-analysis of case-control studies. *Psychiatry Res*. 2018;270:786–791.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (4th Ed., Text Rev.)*. Arlington, VA: American Psychiatric Association; 2000. doi:10.1176/appi.books.9780890423349
17. Jablensky A. Epidemiology of schizophrenia: the global burden of disease and disability. *Eur Arch Psychiatry Clin Neurosci*. 2000;250(6):274–285.
18. Wells GA, Shea B, Oconnell D, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis*. University of Ottawa, Canada; 2012. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed April 9, 2019.
19. Schwarzer G. meta: An R package for meta-analysis. *R news*. 2007;7(3):40–45.
20. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28(2):105–114.
21. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14:25.
22. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. *J Clin Epidemiol*. 2011;64(11):1187–1197.

23. Ascaso FJ, Rodriguez-Jimenez R, Cabezón L, et al. Retinal nerve fiber layer and macular thickness in patients with schizophrenia: influence of recent illness episodes. *Psychiatry Res*. 2015;229(1-2):230–236.
24. Celik M, Kalenderoglu A, Karadag AS, Egilmez OB, Han-Almis B, Şimşek A. Decreases in ganglion cell layer and inner plexiform layer volumes correlate better with disease severity in schizophrenia patients than retinal nerve fiber layer thickness: Findings from spectral optic coherence tomography. *Eur Psychiatry*. 2016;32:9–15. doi:10.1016/j.eurpsy.2015.10.006
25. Chu EM, Kolappan M, Barnes TR, Joyce EM, Ron MA. A window into the brain: an in vivo study of the retina in schizophrenia using optical coherence tomography. *Psychiatry Res*. 2012;203(1):89–94.
26. Lee WW, Tajunisah I, Sharmilla K, Peyman M, Subrayan V. Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: evidence from optical coherence tomography. *Invest Ophthalmol Vis Sci*. 2013;54(12):7785–7792.
27. Topcu-Yilmaz P, Aydin M, Ilhan BC. Evaluation of retinal nerve fiber layer, macular, and choroidal thickness in schizophrenia: spectral optic coherence tomography findings. *Psychiat Clin Psych*. 2018;29(1):28–33. doi:10.1080/24750573.2018.1426693
28. Yılmaz U, Küçük E, Ülgen A, et al. Retinal nerve fiber layer and macular thickness measurement in patients with schizophrenia. *Eur J Ophthalmol*. 2016;26(4):375–378. doi:10.5301/ejo.5000723
29. Khalil MA, Saleh AA, Gohar SM, Khalil DH, Said M. Optical coherence tomography findings in patients with bipolar disorder. *J Affect Disord*. 2017;218:115–122.
30. Polo V, Satue M, Gavin A, et al. Ability of swept source OCT to detect retinal changes in patients with bipolar disorder. *Eye*. 2018;11:1–8. doi:10.1038/s41433-018-0261-6
31. Silverstein SM, Paterno D, Cherneski L, Green S. Optical coherence tomography indices of structural retinal pathology in schizophrenia. *Psychol Med*. 2018;48(12):2023–2033.
32. Garcia-Martin E, Gavin A, Garcia-Campayo J, et al. Visual function and retinal changes in patients with bipolar disorder. *Retina*. 2018. doi:10.1097/IAE.0000000000002252
33. Kalenderoglu A, Sevgi-Karadag A, Celik M, Egilmez OB, Han-Almis B, Ozen ME. Can the retinal ganglion cell layer (GCL) volume be a new marker to detect neurodegeneration in bipolar disorder? *Compr Psychiatry*. 2016;67(C):66–72. doi:10.1016/j.comppsych.2016.02.005
34. Mehraban A, Samimi SM, Entezari M, Seifi MH, Nazari M, Yaseri M. Peripapillary retinal nerve fiber layer thickness in bipolar disorder. *Graefes Arch Clin Exp Ophthalmol*. 2016;254(2):365–371.
35. Petzold A, Wong S, Plant GT. Autoimmunity in visual loss. *Handb Clin Neurol*. 2016;133:353–376.
36. Dinkin M. Trans-synaptic retrograde degeneration in the human visual system: slow, silent, and real. *Curr Neurol Neurosci Rep*. 2017;17(2):16.
37. Dorph-Petersen KA, Lewis DA. Postmortem structural studies of the thalamus in schizophrenia. *Schizophr Res*. 2017;180:28–35.
38. Cho KIK, Kwak YB, Hwang WJ, et al. Microstructural changes in higher-order nuclei of the thalamus in patients with first-episode psychosis. *Biol Psychiatry*. 2019;85(1):70–78.
39. Ng WX, Lau IY, Graham S, Sim K. Neurobiological evidence for thalamic, hippocampal and related glutamatergic abnormalities in bipolar disorder: a review and synthesis. *Neurosci Biobehav Rev*. 2009;33(3):336–354.
40. Haijma SV, Van Haren N, Cahn W, Koolschijn PCMP, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull*. 2012;39(5):1129–1138.
41. Samani NN, Proudlock FA, Siram V, et al. Retinal layer abnormalities as biomarkers of schizophrenia. *Schizophr Bull*. 2018;44(4):876–885.
42. Zarei R, Anvari P, Eslami Y, et al. Retinal nerve fibre layer thickness is reduced in metabolic syndrome. *Diabet Med*. 2017;34(8):1061–1066.
43. Saidha S, Syc SB, Durbin MK, et al. Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness. *Mult Scler*. 2011;17(12):1449–1463.
44. Green AJ, McQuaid S, Hauser SL, Allen IV, Lyness R. Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration. *Brain*. 2010;133(Pt 6):1591–1601.
45. Sekar A, Bialas AR, de Rivera H, et al. Schizophrenia risk from complex variation of complement component 4. *Nature*. 2016;530(7589):177–183. doi:10.1038/nature16549
46. Ehrlich R, Harris A, Moss AM. Anatomy and regulation of the optical nerve blood flow. In: Dartt D, Besharse J, Dana R, eds. *Encyclopedia of the Eye*. New York: Elsevier; 2010:73–82.