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REVIEW ARTICLE

A systematic review and meta-analysis of optical coherence tomography studies in schizophrenia, bipolar disorder and major depressive disorder

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ABSTRACT

Objectives: Due to the common neurodevelopmental origin and easy accessibility, the retina serves as a surrogate marker for changes in the brain. Hence, Optical Coherence Tomography (OCT), a tool to examine the neuronal layers of retina has gained importance in investigating psychiatric disorders. Several studies in the last decade have reported retinal structural alterations in schizophrenia (SCZ), bipolar disorder (BD), and major depressive disorder (MDD). However, the findings are inconsistent. Hence, we conducted a meta-analysis to investigate alterations in OCT parameters in patients with SCZ, BD and MDD.

Methods: We searched electronic databases for studies that examined OCT parameters in patients with SCZ, BD and MDD published up to January 2023. The primary outcome measures were thickness and volumes of the retinal Nerve Fibre Layer (RNFL). We conducted meta-analysis using a random effects model.

Results: The searches yielded 2638 publications of which 43 studies were included in the final analysis across all disorders. Compared to controls, the RNFL was thinner in SCZ patients (SMD $= -0.37$, $p = <0.001$) and BD patients (SMD $= -0.67$, $p = < 0.001$), but not in MDD patients (SMD $= -0.08$, $p = 0.54$). On quadrant wise analysis, temporal quadrant RNFL was thinner in SCZ but not in BD, while all other quadrants were thinner in both SCZ and BD.

Conclusion: We found significant reductions in RNFL thickness in SCZ and BD, but not in MDD. The differential involvement in various quadrants and parameters across the disorders has potential implications for using retinal parameters as a diagnostic biomarker.

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KEYWORDS
Psychosis; retina; optical coherence tomography; mood disorder

1. Introduction

The retina is an integral part of the central nervous system (CNS) and shares a common embryonic origin with the brain. The retina is a direct extension of the brain through the optic nerve and shares many structural and functional similarities with the brain (Hoon et al. 2014). Thus, changes in the retina may be used as surrogate markers to understand changes in the brain. For example, brain cortical atrophy is associated with thinning of retinal neuronal layers (London et al. 2013). Optical Coherence Tomography (OCT) is a non-invasive device used to assess various retinal layers including the nerve fibre layers and the choroid in high resolution. In addition to its utility in ophthalmic conditions (Adhi and Duker 2013), OCT is an extremely useful tool to examine abnormalities in the retinal layers in various neurologic conditions like Alzheimer's disease (Lu et al. 2010), multiple sclerosis (Almarcegui et al. 2010) and Parkinson's disease (Yu et al. 2014).

Among the psychiatric disorders, most studies have examined the retinal nerve fibre layers in schizophrenia (SCZ). Some of these studies report a thinning of the peripapillary Retinal Nerve Fibre Layer (RNFL) in schizophrenia (Lee et al. 2013; Ascaso et al. 2015; Yılmaz et al. 2016), but few studies also report normal RNFL thickness in SCZ (Chu et al. 2012; Mota et al. 2015; Silverstein et al. 2018; Topcu-Yilmaz et al. 2019; Bannai et al. 2020; Jerotic et al. 2020; Miller et al. 2020; Friedel et al. 2022). Similarly, the results about thinning in different retinal quadrants and other parameters including Macular

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volume (MV) and thickness (MT), Cup/Disc ratio (C/D), Outer nuclear layer (ONL) and Inner nuclear layer (INL) are inconsistent (Chu et al. 2012; Lee et al. 2013; Celik et al. 2016; Silverstein et al. 2018). Bipolar Disorder (BD) shares many neurobiological phenotypes with schizophrenia (Tamminga et al. 2013). A few studies have reported RNFL abnormalities in BD as well, similar to SCZ (Khalil et al. 2017; Mehraban et al. 2016; Liu et al. 2021). Finally, a few studies have examined RNFL in Major depressive disorder (MDD) using OCT. While some of these studies reported thinner RNFL in MDD (Jung et al. 2020; Liu et al. 2021), others reported thicker RNFL (Genc et al. 2019) or no difference in thickness (Yildiz et al. 2016; Sönmez et al. 2017). It is important to note that inflammatory processes are known to play an important role in the pathogenesis of different psychiatric disorders, in particular, major depressive disorder and suicidal risk (Serafini et al. 2020). Interestingly, neuroinflammation is also associated with changes in the retina that are detected using OCT (Vujosevic et al. 2023) further supporting the use of the retina as a biomarker.

Considering these disparities in findings, it is desirable to conduct a meta-analysis to collate the existing evidence. Five meta-analyses (Pan et al. 2018; Lizano et al. 2020; Kazakos and Karageorgiou 2020; Komatsu et al. 2022; Gonzalez-Diaz et al. 2022) are published in schizophrenia, with the latest one (Gonzalez-Diaz et al. 2022) assessing studies up to 11 August 2021. Only one previous meta-analysis (Lizano et al. 2020) has examined OCT findings in BD (until December 2018). To the best of our knowledge, no meta-analysis has examined the OCT findings in MDD. Since the publication of these above-mentioned meta-analyses, several new studies have been published which could have an impact on the previous findings. Considering the overlaps and differences between SCZ, BD and MDD we aimed to conduct a meta-analysis to investigate alterations in OCT parameters in patients with SCZ, BD and MDD compared to healthy controls (HC). We aimed to examine Peripapillary RNFL thickness, combined thickness of Ganglion cell layer and Inner plexiform layer (GCL-IPL), MV, MT, CV, C/D, ONL and INL. In addition, we also conducted a meta-analysis of the studies directly comparing the RNFL thickness between SCZ and BD. We conducted a systematic review wherever meta-analysis was not possible due to the limited number of studies.

2. Methods

2.1. Study selection

We included studies that were published in English and met the following inclusion criteria: (a) Cross-sectional or prospective studies that compared OCT parameters between healthy controls and subjects with a diagnosis of SCZ or BD or MDD as diagnosed by DSM-4 or DSM-5 or ICD-10 or by a psychiatrist. (b) Subjects and healthy controls aged 18 years or older. (c) Necessary data available in the studies and reported in the form of mean and Standard Deviations (SDs). Studies were included regardless of treatment status and those with limited data about the OCT parameters were excluded. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (Stang 2010) which uses a rating system (out of a total score of 9) to judge quality based on three elements of a study: selection, comparability, and outcome or exposure. Studies with Newcastle-Ottawa Scale scores $\geq$6, suggesting a relatively high quality, were included. Two independent raters (AP and VK) rated the studies for quality assessment, and disagreements were resolved by discussion. This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (Moher et al. 2009). The PRISMA flow diagram is given in Figure 1. The study was registered in the PROSPERO database (Number-CRD 42022325699).

2.2. Data sources

The studies were identified through PubMed search using the keywords–'schizophrenia OR psychosis OR bipolar disorder OR depressive disorder OR depression' AND 'optical coherence tomography OR retinal nerve fiber layer thickness OR RNFL OR macula volume OR macular thickness OR ganglion cell layer OR choroidal layer OR Outer nuclear layer OR Inner nuclear layer'. The exact keywords were also used to search the Cochrane library and the initial pages of Google Scholar. The databases were searched for articles from their dates of inception to 30 April 2022. We later extended our search to 31 January 2023 as suggested in the peer review process. Titles and abstracts from the search results were examined to ascertain whether they fulfilled the inclusion criteria. The selected articles were also scanned for cross-references that fulfilled our inclusion criterion. Two authors independently screened the titles and/or abstracts of the studies retrieved using the search strategy. The full texts of potentially relevant studies were also retrieved and independently assessed for eligibility.

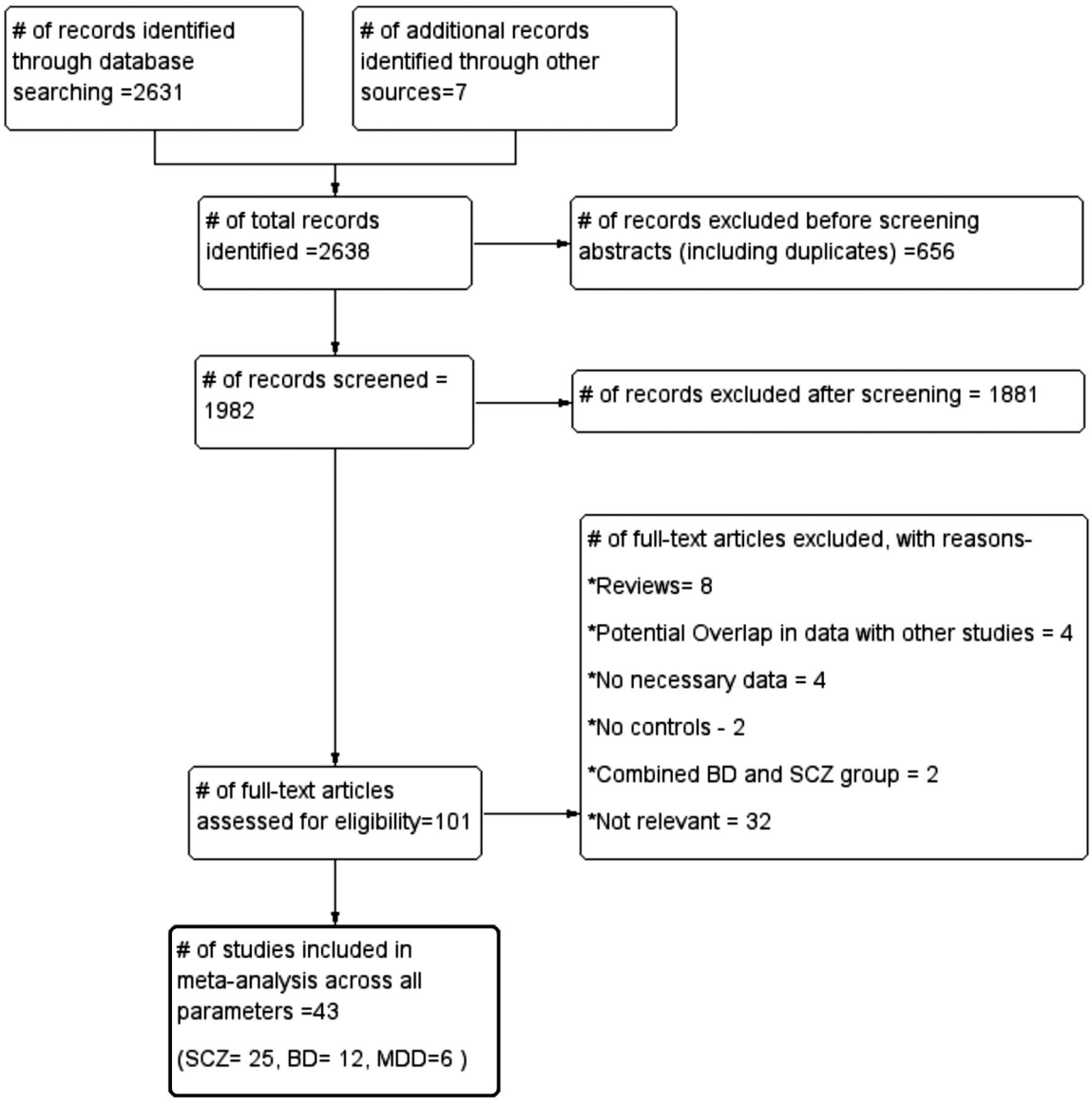

Figure 1. PRISMA flow diagram of database search.

2.3. Outcome measures, data extraction, and meta-analysis

The primary outcome measures were the means and standard deviations of the thickness and volumes of Retinal Nerve Fibre Layer (RNFL) of one or the mean of both eyes (when provided), as measured by OCT. The parameters examined in the meta-analysis included- RNFL thickness and volume (Peripapillary Retinal nerve fibre layer), GCL-IPL thickness and volume (combined Ganglion cell layer and Inner plexiform layer), MV (Macular Volume), MT (Macular Thickness), cup volume and C/D (Cup/Disc) ratio. If these variables were not mentioned in the articles, the data was collected either by extracting it from the figures or by contacting the authors. Additional collected data, when provided, included the number of eyes, sex, age, illness stage, disease duration, symptom severity score, medication status, and OCT device/type. Data from each included study was independently extracted by a set of two authors (AP and VK). Discrepancies were identified and resolved through discussion with a third author (NPR) wherever necessary. A standardised, pre-piloted form was used to extract data from the included studies for evidence synthesis.

We used the statistical package Comprehensive Meta Analysis 3 (CMA 3) to do the meta-analysis. The meta-analysis was performed if at least 3 data sets of control and subject groups were available for that particular measure/design. For each study, we calculated the Standardised Mean Difference (SMD) with a 95% confidence interval using the means and standard deviations of the patient and control groups. Meta-analytic methods were applied to obtain the combined effect size.

SMD with 95% confidence interval was used to combine studies that measured the same outcome even if different methods were used. The outcome measure was calculated using a random-effect model. The results were described narratively wherever meta-analysis was not possible. Assessment of heterogeneity was conducted using the I^2 score with scores greater than 25, 50, and 75% corresponding to low, moderate, and high heterogeneity respectively, and I^2 score $<$ 25% was considered acceptable (Higgins et al. 2003). A study was considered an outlier if the study's confidence interval did not overlap with the confidence interval of the pooled effect size (Harrer et al. 2021). Sensitivity analysis was conducted using leave-one-out analysis to assess whether a single study influenced summary effect size. The potential publication bias was evaluated using Egger's test with a p-value less than 0.05 suggesting significant publication biases. A meta-regression analysis was performed to assess the effects of age, sex, disease duration, the severity of psychiatric symptoms, antipsychotic dosage (chlorpromazine equivalent, mg/day), OCT type, and Newcastle-Ottawa scale (NOS) score on retinal parameters which showed a significant difference in meta-analysis and had at least 10 data sets (Geissbühler et al. 2021). Statistical significance was set at $p < 0.05$ for the meta-regression analysis.

3. Results

The searches across databases, including cross-references, yielded 2638 studies of which 1982 were screened after excluding duplicates. After excluding irrelevant studies, the full texts of 101 studies were screened and 49 studies were included in the systematic review. After further exclusions, 43 studies were included in the final quantitative meta-analysis across all conditions (Figure 1). Four studies were excluded due to potential overlap with other included studies (Cabezon et al. 2012; Jerotic et al. 2020; Zhou et al. 2021; Liu et al. 2022), four studies were excluded due to necessary data not being provided (Samani et al. 2018; Guclu et al. 2018; Orum et al. 2020; Orduna-Hospital et al. 2021), two studies were excluded as they had a combined SCZ and BD sample (Joe et al. 2018; Bannai et al. 2020) and two studies was excluded as it did not have control subjects (van der Heide et al. 2021; Hsu et al. 2022). The number of datasets used for the analysis in each condition and OCT parameter has been described below under their respective headings (See supplementary material and figures of forest plot of respective analysis for further details). The findings of leave-one-out analysis and meta-regression for each parameter have been mentioned if there were significant findings. The socio-demographic details, clinical measures, OCT device type, country of study, and NOS scores have been described in the supplementary material (Supplementary material tables S1–S4).

3.1. Peripapillary RNFL thickness

Twenty-three studies (Supplementary table S0) compared the overall average RNFL thickness between 1899 eyes of patients with SCZ and 1516 eyes of healthy controls. Compared to controls, the RNFL was thinner in SCZ patients (SMD $= -0.37$, 95%CI (-0.50 to -0.23), $p =<$ 0.001) (Figure 2). The I^2 value was 72% indicating moderate heterogeneity. Egger's test suggested a publication bias ($p = 0.03$) and Rosenthal's fail-safe N was 611. Sensitivity analysis by leave-one-out analysis revealed that none of these studies had a significant influence on the summary effect size (Supplementary figure S1). The meta-regression showed that none of the variables including age, sex, illness duration, the severity of symptoms, antipsychotic dose, NOS scores, and OCT device type had a significant influence on the findings.

Twelve studies (Supplementary figure S0) compared the overall average RNFL thickness between 831 eyes of patients with BD and 1276 eyes of healthy controls. Compared to controls, the RNFL was thinner in BD patients (SMD $= -0.67$, 95%CI (-0.99 to -0.36), $p =<$ 0.001, $I^2 =$ 90%,Egger's $p = 0.44$) (Figure 3). Sensitivity analysis by leave-one-out analysis revealed that none of these studies had a significant influence on the summary effect size (Supplementary figure S2). There were no significant findings on meta-regression.

Two studies (Altun et al. 2020; Koman-Wierdak et al. 2021) directly compared RNFL thickness between patients with SCZ and BD. 188 eyes of patients with SCZ and 216 eyes of patients with BD were compared. There was no difference in RNFL thickness between the two groups (SMD $= 0.16$, 95%CI (-0.12 to 0.44), $p = 0.27$, $I^2 = 0\%$) (Supplementary figure S3).

Six studies (Supplementary figure S0) compared the overall average RNFL thickness between 534 eyes of patients with MDD and 913 eyes of healthy controls. There was no difference in RNFL thickness between the two groups (SMD $= -0.08$, 95%CI (-0.36 to 0.19), $p = 0.54$, $I^2 =$ 79%,Egger's $p = 0.03$) (Figure 4). Sensitivity analysis by leave-one-out analysis revealed that one study (Genc et al. 2019) had a significant impact on summary effect size, as the SMD showed that average RNFL thickness was thinner in MDD patients (SMD $= -0.25$, 95%CI (-0.38 to -0.12), $p =<$ 0.001) on leaving out this study (Supplementary

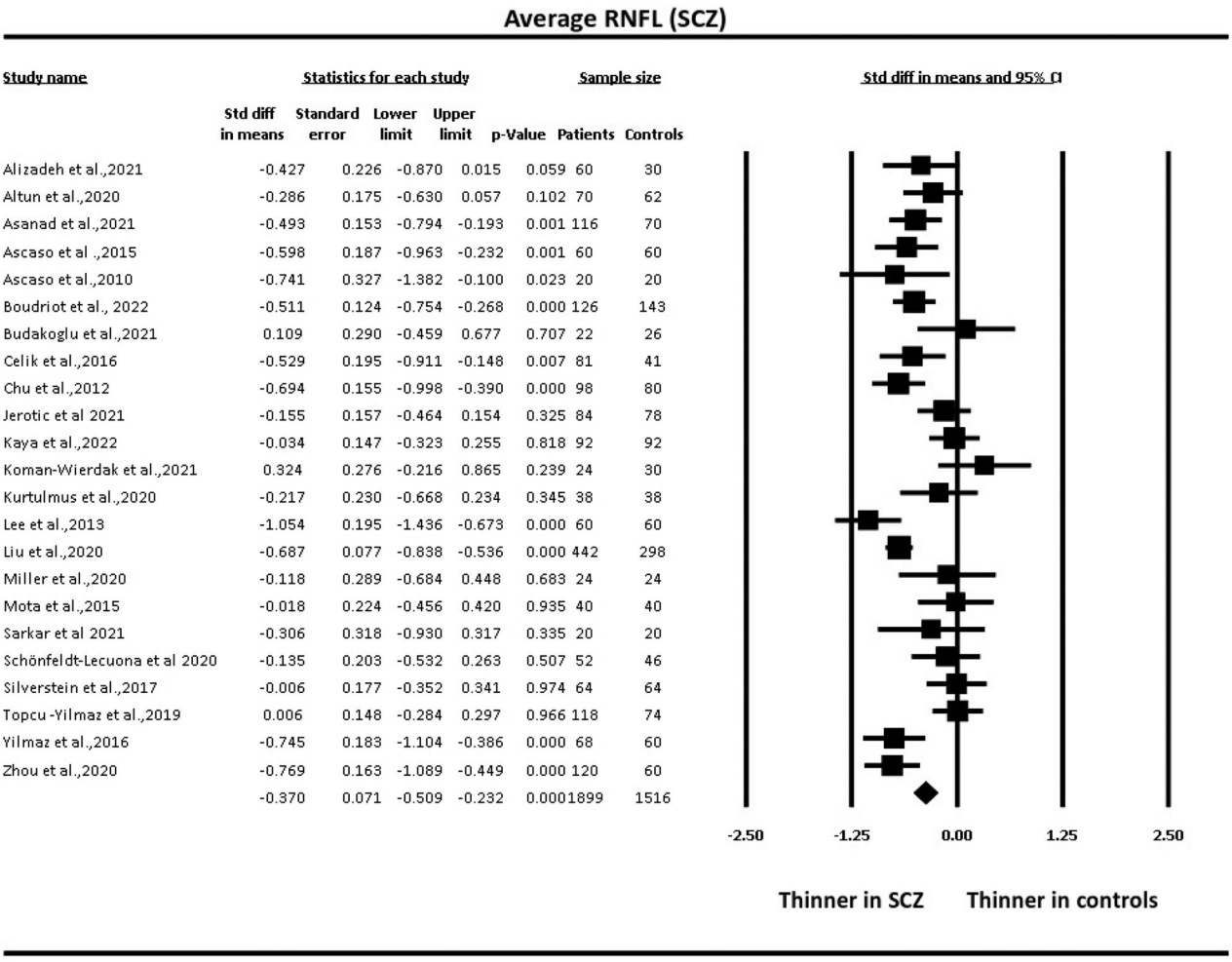

Figure 2. Forest plot showing average RNFL thickness in SCZ vs HV.

figure S4). The rest of the studies did not have an impact on the summary effect size.

3.2. Quadrant-wise peripapillary RNFL thickness

Quadrant-wise peripapillary RNFL thickness was compared between the groups wherever reported.

i. *Superior RNFL*–Fourteen studies (Supplementary figure S0) compared 1432 eyes of SCZ patients and 1195 eyes of healthy controls and found significant reductions in thickness in patients (SMD $= -0.33$, 95%CI (-0.48 to -0.18), $p =< 0.001$, $I^2 = 66\%$, Egger's $p = 0.07$) (Supplementary figure S5). Eight studies (Supplementary figure S0) compared 523 eyes of BD patients and 948 eyes of healthy controls and found significant reductions in thickness in patients (SMD $= -0.50$, 95%CI (-0.71 to -0.29), $p =< 0.001$, $I^2 = 64\%$, Egger's $p = 0.40$) (Supplementary figure S5). Four studies (Supplementary figure S0) compared 274 eyes of MDD patients and 753 eyes of healthy controls and found no significant difference between the two groups (SMD $= -0.11$, 95%CI (-0.51 to 0.29), $p = 0.58$, $I^2 = 84\%$, Egger's $p = 0.02$) (Supplementary figure S5).

ii. *Inferior RNFL*–Fourteen studies (Supplementary figure S0) compared 1432 eyes of SCZ patients and 1195 eyes of healthy controls and found significant reductions in thickness in patients (SMD $= -0.31$, 95% CI (-0.49 to -0.12), $p = 0.001$, $I^2 = 79\%$, Egger's $p = 0.06$) (Supplementary figure S6). Meta-regression showed that higher age was associated with lower inferior RNFL thickness. Five studies (Supplementary figure S0) compared 390 eyes of BD patients and 788 eyes of healthy controls and found significant reductions in thickness in patients (SMD $= -0.55$, 95%CI (-0.71 to -0.40), $p =< 0.001$, $I^2 = 17\%$, Egger's $p = 0.17$) (Supplementary figure S6). Four studies (Supplementary figure S0) compared 274 eyes of MDD patients and 753 eyes of healthy controls and found no significant difference between the

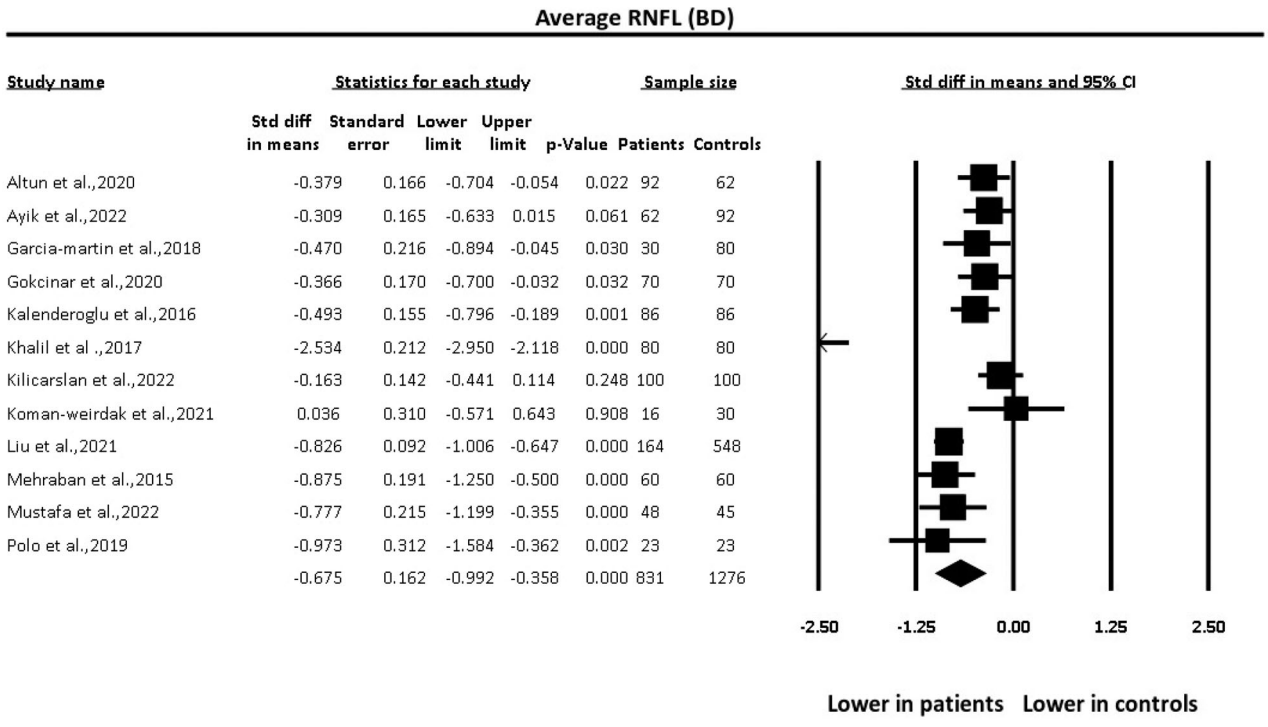

Figure 3. Forest plot showing average RNFL thickness in BD vs HV.

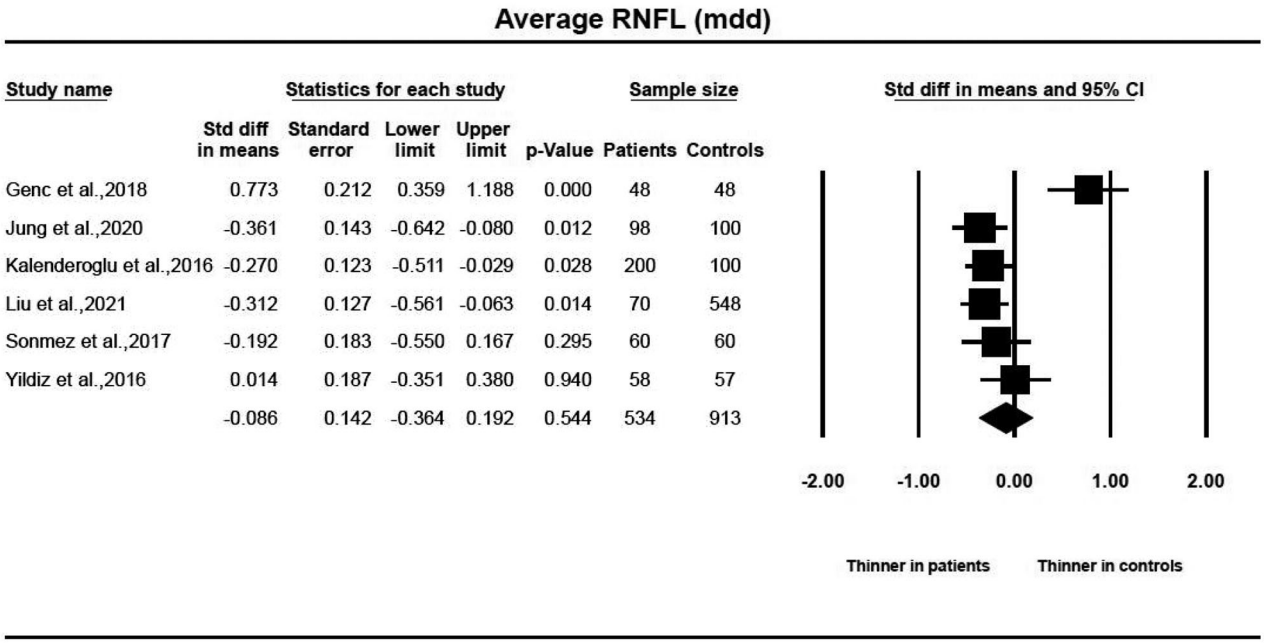

Figure 4. Forest plot showing average RNFL thickness in MDD vs HV.

two groups (SMD= -0.05, 95% CI (−0.49 to 0.37), $p = 0.78$, $I^2 = 86\%$, Egger's $p = 0.02$) (Supplementary figure S6).

iii. *Temporal RNFL*–Eighteen studies (Supplementary figure S0) compared 1422 eyes of SCZ patients and 1211 eyes of healthy controls and found significant reductions in thickness in patients (SMD = −0.10, 95% CI (−0.17 to −0.02), $p = 0.01$, $I^2 = 0\%$, Egger's $p = 0.48$) (Supplementary figure S7). 4/18 studies had significant impact on summary effect size on leave-one-out analysis (Supplementary material table S7). Eleven studies

(Supplementary figure S0) compared 667 eyes of BD patients and 728 eyes of healthy controls and found no significant difference between the two groups (SMD = −0.01, 95%CI (−0.01 to 0.96), $p = 0.84$, I^2 = 0%, Egger's $p = 0.33$) (Supplementary figure S7). Three studies (Supplementary figure S0) compared 204 eyes of MDD patients and 205 eyes of healthy controls and found no significant difference between the two groups (SMD = −0.01, 95%CI (−0.20 to 0.18), $p = 0.89$, I^2 = 0%, Egger's $p = 0.25$) (Supplementary figure S7).

iv. *Nasal RNFL*–Eighteen studies (Supplementary figure S0) compared 1422 eyes of SCZ patients and 1211 eyes of healthy controls and found a significant reduction in thickness in patients (SMD = −0.23, 95% CI (−0.45 to 0.01), $p = 0.04$, I^2 = 87%, Egger's $p = 0.34$) (Supplementary figure S8). 7/18 studies had significant impact on summary effect size on leave-one-out analysis (Supplementary material table S7). Eleven studies (Supplementary figure S0) compared 667 eyes of BD patients and 728 eyes of healthy controls and found significant reductions in thickness in patients (SMD = −0.23, 95%CI (−0.38to-0.08), $p = 0.003$, I^2 = 46%, Egger's $p = 0.22$) (Supplementary figure S8). Three studies (Supplementary figure S0) compared 204 eyes of MDD patients and 205 eyes of healthy controls and found no significant difference between the two groups (SMD = −0.02, 95% CI (−0.34 to 0.39), P-0.89, I^2 = 70%, Egger's $p = 0.17$) (Supplementary figure S8).

3.3. GCL-IPL parameters

Seven studies (Supplementary figure S0) analysed GCL-IPL with a total of 380 eyes from SCZ and 336 eyes from HC and found a significant reduction of GCL-IPL thickness in SCZ (SMD = −0.47, 95%CI = −0.63 to −0.30, $p =< 0.001$, I^2 = 16%, Egger's $p = 0.48$) (Supplementary figure S9). One study reported GCL and IPL findings separately and found significantly lower IPL thickness but not GCL thickness in patients with SCZ (Kurtulmus et al. 2020).

Two studies reported GCL-IPL in BD (Khalil et al. 2017; Polo et al. 2019) and two studies reported GCL-IPL thickness in MDD (Yildiz et al. 2016; Jung et al. 2020), and none of these studies found a significant difference in thickness between patient groups and controls. One study (Kalenderoglu et al. 2016) in MDD reported GCL and IPL volumes separately and found significantly reduced volumes in MDD patients compared to controls. The volumes were also significantly smaller in patients with recurrent depression than in those with the first episode.

3.4. Macular thickness and volume

Thirteen studies (Supplementary figure S0) analysed MT with a total of 1005 eyes from SCZ and 827 eyes from HC and found significant reduction of MT in SCZ (SMD = −0.59, 95% CI = −0.82 to −0.37, $p =< 0.001$, I^2 = 80%, Egger's $p = 0.13$) (Supplementary figure S10). Four studies (Supplementary figure S0) analysed MT with a total of 328 eyes from BD and 723 eyes from HC and found significant reduction of MT in BD (SMD = −0.68, 95% CI = −1.29 to −0.08, $p = 0.02$, I^2 = 92%, Egger's $p = 0.21$) (Supplementary figure S10). Two studies (Yildiz et al. 2016; Liu et al. 2021) reported MT in MDD and neither of these studies found a significant difference in thickness between MDD and controls.

Twelve studies (Supplementary figure S0) analysed MV with a total of 718 eyes from SCZ and 660 eyes from HC and found a significant reduction of MV in SCZ (SMD = −0.53, 95%CI = −0.75 to −0.30, $p =< 0.001$, I^2 = 74%, Egger's $p = 0.11$) (Supplementary figure S11). Meta-regression showed that higher NOS scores were associated with lower MV. None of the BD studies reported MV. One study (Yildiz et al. 2016) reported MV in MDD and this study did not find a significant difference in MV between MDD and controls.

3.5. Cup volume and cup/disc (C/D) ratio

Three studies (Supplementary figure S0) analysed cup volume with a total of 590 eyes from SCZ and 440 eyes from HC and found significantly higher cup volumes in SCZ (SMD = 0.32, 95% CI = 0.09–0.54, $p = 0.004$, I^2 = 52%, Egger's $p = 0.27$) (Supplementary figure S12). One study (Liu et al. 2021) reported cup volumes in BD and found no difference in cup volumes between BD and controls. Two studies reported cup volumes in MDD. One study (Liu et al. 2021) found increased cup volumes in MDD, while the other (Jung et al. 2020) did not find any difference between MDD and controls. Four studies (Supplementary figure S0) analysed C/D ratio with a total of 190 eyes from SCZ and 188 eyes from HC and found no significant difference in C/D ratio between the two groups (SMD = 0.33, 95% CI = −0.06–0.71, $p = 0.10$, I^2 = 68%, Egger's $p = 0.49$). (Supplementary figure S13). 1/4 studies had significant impact on summary effect size on leave-one-out analysis (Supplementary material table

S7). Meta-regression showed that higher NOS scores was associated with higher C/D ratio. None of the BD studies reported on the C/D ratio. One MDD study (Jung et al. 2020) reported on C/D ratio and it did not find any difference between MDD and controls.

3.6. Outer and Inner nuclear layers

One study (Schönfeldt-Lecuona et al. 2020) found significant reduction in ONL thickness in patients with SCZ, but only in the outer regions of the right eye. Reduced ONL thickness in the foveal and parafoveal regions was reported in two other studies (Samani et al. 2018; Friedel et al. 2022). We did not find any studies reporting ONL findings in BD and MDD.

INL total volume reduction in the left eye of SCZ patients was reported by one study (Schönfeldt-Lecuona et al. 2020) while two other studies (Samani et al. 2018; Friedel et al. 2022) did not find any significant changes in INL thickness in patients with SCZ. In BD, one study (Garcia-Martin et al. 2019) reported thickening of INL in patients when compared to controls. No studies were found that reported INL findings in MDD.

3.7. Relationship with course of illness

In SCZ, several studies have shown RNFL, MT, MV to be negatively correlated with illness duration (Lee et al. 2013; Mota et al. 2015; Schönfeldt-Lecuona et al. 2020). In BD, studies have shown a negative correlation of illness duration with RNFL, GCL-IPL (Mehraban et al. 2016; Gokcinar et al. 2020; Orduna-Hospital et al. 2021). Duration of current depressive episode negatively correlated with GCL-IPL and nasal RNFL thickness in MDD (Yildiz et al. 2016). GCL-IPL and global RNFL thickness were also found to be significantly lower in patients with recurrent depressive episodes than first-episode patients. (Kalenderoglu et al. 2016).

3.8. Relationship with clinical features

In SCZ, PANSS scores negatively correlated with GCL-IPL thickness (Celik et al. 2016), while lower MV correlated with the severity of positive symptoms but not negative symptoms (Chu et al. 2012). Cognitive symptoms on the other hand were negatively correlated with RNFL and positively correlated with cup volume and C/D ratio (Liu et al. 2020). Treatment-resistant patients had lower GCL-IPL and choroidal thickness but had no difference in RNFL compared to treatment-responsive patients (Celik et al. 2016; Orum et al. 2020: Kango et al. 2022). In BD, GCC thickness was increased in all quadrants compared to controls but there was no difference in thickness between the euthymic, manic, and depressive groups (Cokunlu et al. 2022). In MDD, lower RNFL thickness was associated with a higher incidence of depressive symptoms (van der Heide et al. 2021).

3.9. Relationship with psychotropics

In SCZ, there was a negative correlation between antipsychotic dose and nasal RNFL (Altun et al. 2020), but no difference was found in RNFL thickness between those on First Generation Antipsychotics (FGAs) and Second Generation Antipsychotics (SGAs) (Altun et al. 2020). In MDD, the duration of SSRI use was correlated with a reduction in parafoveal GCC and foveal thickness (Guclu et al. 2018).

3.10. OCT findings in first-degree relatives (FDRs)

Two studies (Kurtulmus et al. 2020; Kaya et al. 2022) investigated retinal parameters in FDRs of patients with SCZ and found no difference in RNFL compared to controls. One of the studies (Kurtulmus et al. 2020) found significantly reduced IPL thickness in FDRs when compared to healthy controls while the other (Kaya et al. 2022) found a trend with lowest GCL-IPL thickness in patients and the highest in controls. In BD, one study (Ayik et al. 2022) found significant reduction in GCL-IPL in both patients and FDRs compared to controls, while another study (Kilicarslan et al. 2022) found central MT to be lower in patients and FDRs compared to controls, although the difference between FDRs and controls was not statistically significant. No studies have examined OCT parameters in FDRs of MDD patients to our knowledge.

A more detailed description of the findings on clinical variables and OCT parameters is given in the supplementary material section S1.

4. Discussion

The findings of the meta-analysis suggest a significant reduction in peripapillary RNFL thickness in patients with SCZ and BD, but not in those with MDD. These findings were replicated in superior, inferior and nasal quadrants when RNFL thickness was analysed based on quadrants. However, in the temporal quadrant, RNFL was thinner in SCZ but not in BD. SCZ and BD patients did not differ from each other on direct head-to-head comparison in terms of average RNFL

thickness. A significant reduction in GCL-IPL, MT, MV and a significant increase in cup volume and C/D ratio was also found in SCZ.

These findings replicate the findings of previous meta-analyses in SCZ (Pan et al. 2018; Lizano et al. 2020; Kazakos and Karageorgiou 2020; Gonzalez-Diaz et al. 2022; Komatsu et al. 2022). The meta-analysis by Komatsu and colleagues (Komatsu et al. 2022) reported global RNFL thinning and thinning in inferior and temporal quadrants only, while the analysis by Gonzalez-Diaz and colleagues reported global and superior quadrant thinning. However, we found thinning in all the quadrants. We also found significant reductions in GCL-IPL, MV, MT and higher C/D ratio and cup volume in SCZ patients like an earlier meta-analysis (Komatsu et al. 2022). On meta-regression, the inferior RNFL was negatively related to age. As with SCZ, patients with BD had significantly lower RNFL thickness compared to controls. On quadrant-wise comparison, BD patients had thinner RNFL in all quadrants except the temporal quadrant. These findings are like the only other meta-analysis of OCT findings in BD (Lizano et al. 2020). MT was also significantly thinner in BD patients compared to controls. We did not have enough studies to perform a meta-analysis for the other OCT parameters in BD. We did not find any significant difference in RNFL thickness between healthy individuals and patients with MDD. From the limited number of studies for the other parameters, we did not find any change in GCL-IPL thickness, MV, MT, C/D ratio, and cup volumes in MDD. As this is the first meta-analysis to examine the OCT parameters in MDD, we could not compare our findings with any previous studies.

An interesting finding was the similarities and differences in RNFL thickness in SCZ and BD. On direct head-to-head comparison of RNFL thickness between SCZ and BD meta-analytically, there was no significant difference in thickness between the two groups. These findings lend support to the idea that these disorders share a common neurobiological phenotype (Tamminga et al. 2013). However, it is important to note that this finding is based on an analysis of a small number of studies. On pairwise meta-analysis of SCZ or BD vs healthy individuals, both SCZ and BD had decreased RNFL thickness in superior, inferior and nasal quadrants, but the thickness of temporal quadrant differed. Thinning of RNFL in the temporal quadrant was seen in SCZ but not in BD. Interestingly, the differential pattern of retinal thinning is attributed to changes in magnocellular and parvocellular pathways. For example, Parkinson's disease is associated with preferential involvement of the parvocellular pathway and RNFL thinning in the temporal quadrant. Alzheimer's disease is associated with the involvement of the magnocellular pathway and RNFL thinning in superior and inferior quadrants. In Multiple System Atrophy (MSA), the magnocellular pathway is involved and temporal RNFL is relatively preserved (La Morgia et al. 2017; Mendoza-Santiesteban et al. 2017). The cell bodies of the P–ganglion cells are concentrated in the macula and the axons of these cells form the nerve fibre layers of the parvocellular pathway. The nerve fibre layers from the P-cells predominantly project to the temporal part of the optic nerve (ON) head in comparison to the nerve fibre layers from the M—cells (magnocellular pathway) which project to the superior, inferior and the nasal quadrants of the ON head (Mendoza-Santiesteban et al. 2017). So, it appears that differential RNFL thickness in SCZ and BD may be due to parvocellular and magnocellular pathway nerve fibres being differentially affected in these disorders with more pronounced impairment in both pathways in SCZ while more prominent impairment in the magnocellular pathway is noted in BD. Behavioural, retinal and neuroimaging studies have reported dysfunctional magnocellular and parvocellular pathways in schizophrenia, though it is less pronounced in the latter than the former (e.g. Butler et al. 2009; Bedwell et al. 2013; Kim et al. 2015; Jahshan et al. 2017). On the other hand, one study reported impaired magnocellular pathway functioning and intact parvocellular pathway function in BD (O'Bryan et al. 2014). Since the functions of the P-cells (visual acuity, colour discrimination, high-frequency contrast sensitivity) and M-cells (movement discrimination, low-frequency contrast sensitivity) are different, comparing the behavioural performances on the specific tasks in SCZ and BD and combining with the structural/functional RNFL alterations in these disorders could provide better power to differentiate the two conditions. As the temporal RNFL and nasal RNFL thinning in SCZ was influenced by individual studies as seen on leave-one-out analysis, these findings need to be taken as preliminary pending replication in the future.

We also found a significant difference between MDD and BD in the pattern of RNFL thinning. While the RNFL thinning was noted in BD, there was no significant difference in MDD. However, one needs to be cautious in interpreting this as the MDD patients included in our analysis had wide variability in terms of severity and number of episodes which might have influenced the findings. The only longitudinal study with a large sample (van der Heide et al. 2021) found a significant association between reduced RNFL

thickness and depressive symptom severity. If the absence of RNFL thickness in MDD is replicated in future studies as well, this could have potential implications in differentiating BD from MDD and immediate therapeutic implications.

The review also suggested a negative correlation between RNFL thickness and disease duration in BD (Mehraban et al. 2016; Gokcinar et al. 2020; Orduna-Hospital et al. 2021). A few neuroimaging studies have shown progressive neurodegenerative changes in BD with volume reduction observed in the thalamus, hippocampus and subgenual prefrontal cortex along with ventricular enlargement (Kempton et al. 2008; Ng et al. 2009). As this inference is based on multiple cross-sectional studies, future longitudinal studies with repeated assessments are needed for definitive conclusions.

The following limitations need to be noted while interpreting the study findings. First, due to the limited number of studies for certain parameters (GCL-IPL. MV, MT, C/D ratio, cup volume), we were unable to conduct a meta-analysis for these parameters in BD and MDD. Second, although we have conducted meta-regression, the number of parameters which had appropriate number of studies (>10) (Geissbühler et al. 2021) was small. Moreover, the limitations of meta-regression with aggregate data, like ecological bias, should also be considered (Thompson and Higgins 2002). Third, the sample size of individual studies is small. Considering the heterogeneity of these disorders, the sample examined may not be representative. Fourth, we have included only English language studies which exclude studies published in other languages. Fifth, there is wide variation in the clinical characteristics of the patients which might influence our findings. Sixth, the heterogeneity estimate is quite high for most of the parameters studied. While we tried to address this by using a random effects model for meta-analysis and performing meta-regression (Cordero and Dans 2021), our findings should be interpreted with this significant limitation in mind. It should also be noted that I^2 may be overestimated in a small meta-analysis like the current study (von Hippel 2015). Seventh, egger's test suggested publication bias for average RNFL findings in SCZ. However, the Rosenthal's failsafe N was large at 611. Future meta-analysis may consider including unpublished and non-English language studies as well. Eighth, few of the parameters had studies having significant impact on summary effect size on leave-one-out analysis. Hence, the results from these parameters should be interpreted with caution. Finally, the type of machine used is different in the various studies, along with the fact that the OCT machine quality has also changed significantly over the course of the period for the studies included should be considered.

5. Conclusion

In conclusion, our meta-analysis found significant reductions in RNFL, MV, MT, and GCL-IPL thickness and an increase in cup volume and C/D ratio in patients with SCZ. In addition, the current study also found significantly thinner RNFL in BD patients, which was not different compared to patients with SCZ on head-to-head comparison. The differential involvement of RNFL in the various quadrants in SCZ and BD could be a useful tool for the diagnosis of these disorders. On the other hand, no significant differences in RNFL thickness were found in MDD patients compared to controls. Studies that directly compare the OCT parameters in SCZ vs BD and BD vs MDD are needed to confirm possible differential involvement in these disorders. More studies that assess the OCT parameters based on the clinical status (i.e. euthymic or manic or depressive episode) are also needed in the future. Longitudinal studies with a repeated examination of the same patients would provide vital clues regarding the temporal stability of these changes, relation with the symptom status, progress with increasing duration of illness, and the effect of medication.

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None.

Author contributions

AP and VK were involved in the literature search, data extraction, data analysis, interpretation of results, and manuscript preparation. PM, AA, RB, TTJMB were involved in the interpretation of results and manuscript preparation. NPR was involved in conceptualisation, data extraction, interpretation of results, and manuscript preparation. All authors approved the final manuscript.

Statement of interest

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