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Inter-device reliability of swept source and spectral domain optical coherence tomography and retinal layer differences in schizophrenia

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INTER-DEVICE RELIABILITY OF SWEPT SOURCE AND SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY AND RETINAL LAYER DIFFERENCES IN SCHIZOPHRENIA

by

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SWETHA GANDU

ABSTRACT

Introduction: Optical coherence tomography (OCT) is used to study retinal structure in schizophrenia. Changes in retinal structure, especially the retinal nerve fiber layer (RNFL) have been correlated with psychotic disorders. Along with a decrease in macular outer nuclear layer (ONL) thickness and an increase in macular outer plexiform layer (OPL). However, measurement variability is a concern for inner retinal layers since there are various generations of OCT devices resulting in differing measurements. We investigated the inter- and intra-device agreement of macular thickness between spectral domain (SD-OCT) and swept source-OCT (SS-OCT), and compared macula and peripapillary group differences in schizophrenia using SS-OCT for inner retinal layers. Additionally, we expanded on our previous work and investigated whether baseline outer retinal layer data for macular ONL and OPL thickness predicted clinical and cognitive changes in individuals with schizophrenia.

Methods: For the inter- and intra-scanner study, macular OCT thickness was obtained for schizophrenia (SZ, n=30) and healthy controls (HC, n= 22) subjects using SD-OCT (Heidelberg Spectralis) and SS-OCT (DRI Topcon Triton). Peripapillary thickness was

obtained using SS-OCT. RNFL, ganglion cell-inner plexiform complex (GCL+), RNFL+ GCL+ (GCL++), and macular thickness were collected. For the longitudinal study, 7 participants diagnosed with either schizophrenia or schizoaffective baseline OCT measurements and clinical measures were obtained for all 7 participants from study 1, along with 6 months follow up clinical measures. OCT measurements for the macular OPL and ONL were gathered using the Heidelberg Spectralis Clinical and cognitive data was gathered. All statistical analyses were performed using R software.

Results: There was excellent inter-scanner agreement for GCL+ and GCL++ with Interclass correlation coefficient (ICC) values between r =0.92-0.99. Good to excellent intra-scanner agreement was present except for macular RNFL in the SS-OCT device. No significant peripapillary group differences were identified. Poorer (Global Assessment of Functioning) GAF scores were correlated with thinner macular layers. Greater mania symptoms were associated with smaller peripapillary GCL+ thickness (r=-0.43, p=0.03). Poor overall cognition was associated with smaller peripapillary retinal thickness (r=0.36, p=0.02). For the longitudinal study, an increase in baseline OPL thickness was correlated with worse positive symptoms according to the Positive and Negative Symptom Severity(PANSS) at the 6 month follow up (r=0.77, p=0.04) with a trend level effect for PANSS total scores (r=0.71, p=0.08). There was no significant correlation between the change in clinical or cognitive outcomes for 6 months and baseline OPL and ONL thickness.

Conclusion: While there is RNFL variability, GCL+ and GCL++ are comparable between scanners SD-OCT and SS-OCT. Given that RNFL thinning is strongly implicated in psychotic disorders, the use of OCT scanners should not be interchanged due to increased RNFL measurement variability. Additionally, though further research is needed on investigating changes in clinical outcomes with changes in OCT measurements, OPL thickness might be a predictor of long-term clinical outcomes or changes in brain pathology for individuals with schizophrenia.

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LIST OF ABBREVIATIONS

ANOVA……Analysis of Variance

BACS……Brief Assessment of Cognition in Schizophrenia

BMI…….……. Body Mass Index

BSNIP-2……Bipolar and Schizophrenia Network on Intermediate Phenotype-2

BU ..... Boston University

CPZ……Chlorpromazine

DSM-IV…….. Diagnostic and Statistical Manual of Mental Disorders IV

EDTRS…….Early Treatment of Diabetic Retinopathy

GAF……Global Assessment of Functioning

GCL++……..Ganglion Cell-Inner Plexiform-Retinal Nerve Fiber Layer

GCL+…….,,,,,, Ganglion Cell – Inner Plexiform Layer

GCL……...Ganglion Cell Layer

ICC……..…….Interclass Correlation Coefficient

IPL……..Inner Plexiform Layer

IRB ..... …..International Review Board

LGN……..…….Lateral Geniculate Nucleus

MADRS……..……Montgomery-Asberg Depression Rating Scale

OCT……Optical Coherence Tomography

OD……..……Right Eye

ONL……. Outer Nuclear Layer

OPL……Outer Plexiform Layer

OS…….……Left Eye

PANSS…….……..…Positive and Negative Symptom Severity

RNFL…….…Retinal Nerve Fiber Layer

SD-OCT……. Spectral Domain Optical Coherence Tomography

SFS……. Birchwood Social Functioning Scale

SS-OCT……. Swept Source Optical Coherence Tomography`

STABLE…….…. Stability of Biotypes: a Longitudinal Evaluation

TD-OCT……Time Domain Optical Coherence Tomography

YMRS…….……Young Mania Rating Score

INTRODUCTION

Schizophrenia

Schizophrenia was coined in 1911, as a reference to dissociation and disruption of thought processes, emotion, and behavior. However in the past century the definition of schizophrenia has changed (Carpenter & Buchanan, 1994). Current neurophysiological models of schizophrenia focus on distributed brain dysfunction with bottom-up (basic perceptual processes) as well as top-down (higher cortical regions) components (Javitt, 2009). Schizophrenia affects 1% of the population (Tomasik et al., 2016). Schizophrenia is not classified by certain symptoms but rather by a group of conditions that have similarities to some psychiatric and non-psychiatric disorders (Carpenter & Buchanan, 1994; Tomasik et al., 2016). Psychosis has become a central theme in the classification of schizophrenia. Those diagnosed with schizophrenia can experience positive or negative symptoms. Positive symptoms are classified as hallucinations, delusions, confused thoughts and disorganized speech, and movement disorders. Whereas negative symptoms are symptoms such as lack of motivations, lack of social interest, inattention to social or cognitive input and being apathetic.

The onset age of schizophrenia is around late adolescence. Psychotic symptoms usually occur between the ages of 17 and 30 for men, however for women it between the ages of 20 and 40 (Carpenter & Buchanan, 1994). There have been various causes proposed for schizophrenia, including genetics, birth and gestational complications, and lastly, winter birth (Carpenter & Buchanan, 1994). Those whose have a parent, grandparent, or

siblings that have been diagnosed with schizophrenia have a ten percent likelihood of getting schizophrenia, whereas if both parents have schizophrenia there is an increased chance of getting schizophrenia (Salleh, 2004). Another risk factor for schizophrenia is winter births. Research has shown that there is an 8% increased risk of getting schizophrenia for winter births (Boyd et al., 1986). Gestational birth complications such as injuries to the fetus are known to increase the risk of schizophrenia, due to a reduction in the supply of oxygen to developing brain regions. The areas of the brain that are affected by hypoxia are the hippocampal and para hippocampal area (Jenkins, 2013).

Currently treatment of schizophrenia exists to help improve positive symptoms, and to stabilize a patient and prevent a relapse. Antipsychotic drugs are used to manage psychosis by reducing hallucinations and delusions and decreasing symptoms such as withdrawal and apathy, and to controls symptom (Correll, 2020). Common antipsychotics that are used are clozapine, chlorpromazine, and haloperidol.

Patients with schizophrenia are known to have abnormalities in the ventricular system along with abnormalities in the temporal lobe, and a decrease in volume in the amygdala and hippocampus (Carpenter & Buchanan, 1994; Harrison, 1999; Tomasik et al., 2016). Imaging studies have shown additionally that brains of individuals with schizophrenia tend to have a reduction in hippocampal and cortical volumes, and large ventricular spaces (Harrison, 1999; Tomasik et al., 2016). These changes that are seen in the brains of schizophrenia are not caused because of drug effects (Tomasik et al., 2016). A meta-analysis analyzing the longitudinal effects of schizophrenia found that depending

on age, positive symptoms vary in the long-term while negative symptoms remain mostly constant. Cognition becomes stable but it may depend on age and medication status. Finally, frontal lobe volume reductions but not temporal lobe reductions are found in the gray and white matter (Heilbronner et al., 2016).

Studies have also shown that cortical atrophy can be a predicted by retinal layer thinning (Bannai et al., 2020; Chu et al., 2012; Lizano et al., 2020; London et al., 2013), as the retina is known to be an extension of the central nervous system, which has led to the use of retinal imaging with OCT to analyze changes in retinal layers of schizophrenia patients, as these changes are not reversible.

Changes in Retinal Layers in Psychosis

The retina is an extension of the diencephalon (Lizano et al., 2020; London et al., 2013). The retina and the brain share many similarities as they both are layered, have neurons, and have glial cells (London et al., 2013). The retina has photoreceptors which are not present in the brain. Additionally, the retina has ten layers. The outer layers of the retina are closer to the choroid and contain most photoreceptor cells, whereas the inner layers of the retina are toward the virtuous. Photoreceptors include rods and cones in the outer retinal layers that convert light into electrical stimuli using neurotransmitters to travel to other retinal layers. Once the impulse passes to bipolar cells it reaches the retinal ganglion cells (Moraes & Gustavo, 2013). The passage of the impulse can be seen in figure 1.The axons of the retinal ganglion cells(RGC)form the optic nerve. There are two optic nerves, one for each eye and these nerves meet at the optic chiasm. At the optic chiasm,

the nerve fibers from the temporal retina of one eye merge with the nasal retinal fibers of the opposite eye. Once the fibers merge, the axons continue to the optic tract and synapse in the Lateral Ganglion Nucleus(LGN). The cells of the LGN communicate with the visual cortex. The LGN is a relay center in the thalamus, and the cells of the LGN communicate with the visual cortex. In figure 2, a detailed image is present to show how the eye could be a window into the brain. Studies have shown that there are reductions in the size of the thalamus in individuals with schizophrenia (Lizano et al., 2020). As they are derived from the same embryonic tissue, alterations in retinal layer morphology have been associated with cortical changes in various neuropsychiatric disorders such as multiple sclerosis (Saidha et al., 2011), Alzheimer's disease (Berisha et al., 2007; Parisi et al., 2001) and schizophrenia (Bannai et al., 2020; Lizano et al., 2020).

Figure 1: Retinal Layer Arrangement. In this model the retinal layers are presented with their neuronal bodies and the interaction among each of the neuronal bodies (*Gray's Clinical Neuroanatomy: The Anatomic Basis for Clinical Neuroscience*).

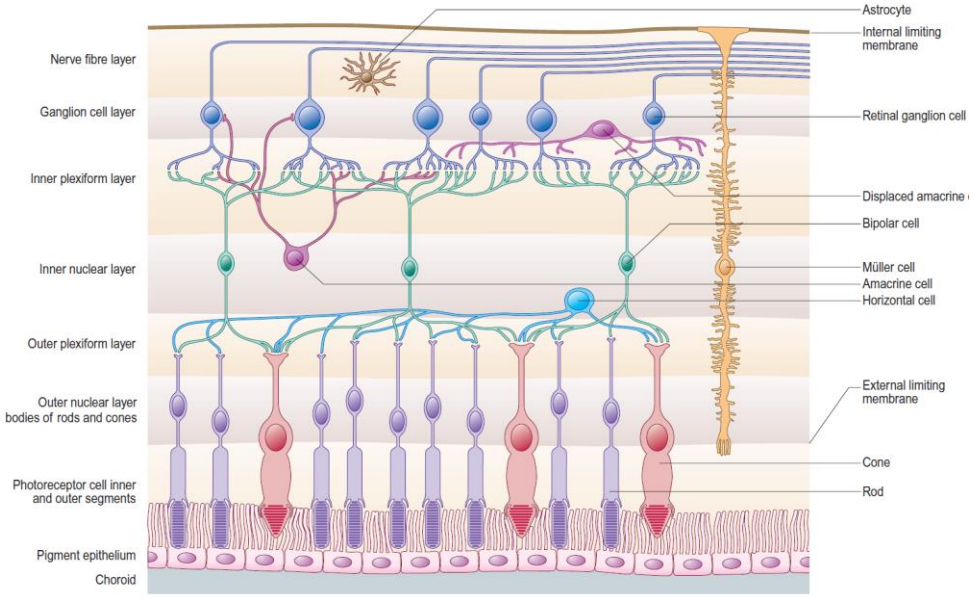
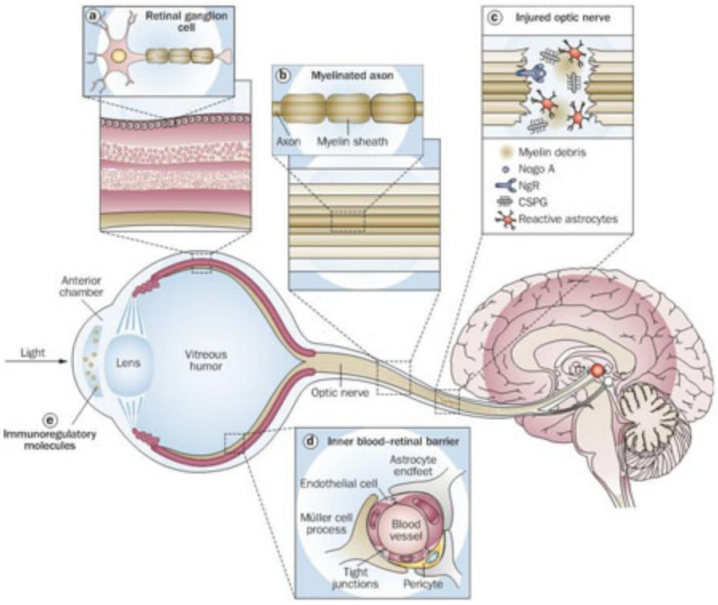
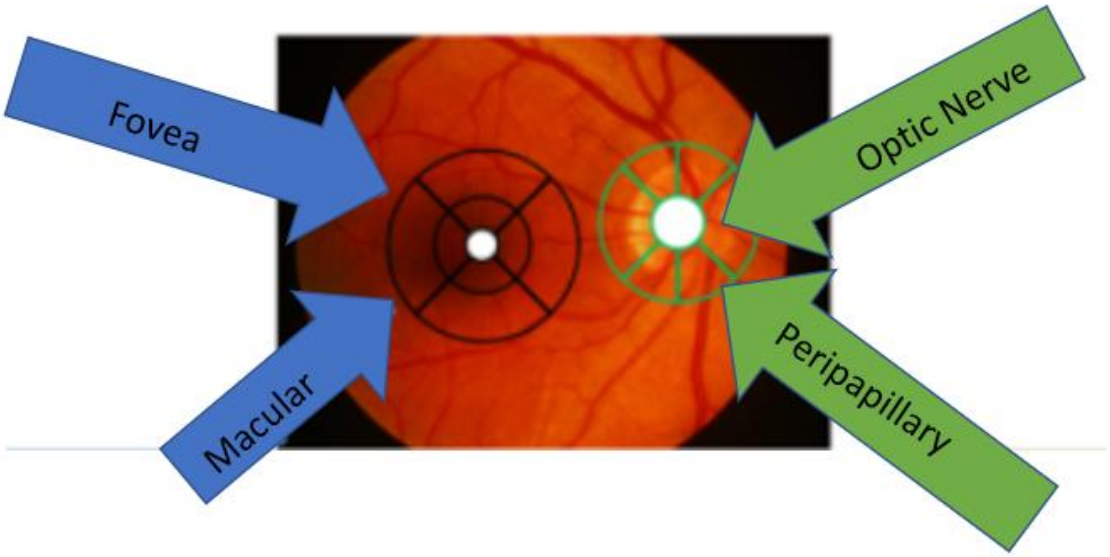


Figure 2: Retinal Connection to the Brain. In this model the connection of the eye to the central nervous system is seen below. Change in retinal thickness and the optic nerve can impact functioning(London et al., 2013).



In previous studies, including a meta- analysis examining retinal cytoarchitectural changes in schizophrenia and bipolar disorder, there was thinner peripapillary retinal nerve fiber layer(RNFL) and Ganglion cell- Inner plexiform layer(GCL+) in individuals with schizophrenia (Lizano et al., 2020). Currently there is mixed evidence on whether retinal thinning is associated with psychosis. (Bannai et al., 2020; Chu et al., 2012; Lizano et al., 2020; Miller et al., 2020; Silverstein et al., 2018). OCT measurements can either be peripapillary or macular, depending on their location, as peripapillary are taken at the optic nerve and macular measures are taken at the fovea (Figure 3). Most studies have explored peripapillary RNFL, but only a few have looked at the macular retinal layers. The RNFL is the inner most retinal layer, consisting of the retinal ganglion cells. The RNFL is known to be a stronger indicator of disease severity compared to other inner retinal layers, as the RNFL is more sensitive to vascular changes caused by inflammation (Green et al., 2010; Lizano et al., 2020).

Figure 3: Fundoscopic image of the eye showing the fovea and optic nerve. The fovea is where macular retinal OCT measurements occur. The optic nerve is where peripapillary OCT measurements occur. (Cavaliere et al., 2019)



GCL+ and GCL++ has also been noticed to have a reduction in thickness in schizophrenia and bipolar disorder (Celik et al., 2016; Lizano et al., 2020). The GCL+ consists of the ganglion cell layer and inner plexiform layer. The GCL++ consist of the GCL+ and the RNFL. In one study, it has been shown that reductions in Ganglion Cell Layer- Inner Plexiform Layer (GCL-IPL)volume can lead to an increase in PANSS scores for schizophrenia (Celik et al., 2016). The GCL+ contains the retinal ganglion cells along with the displaced amacrine cells. GCL-IPL are only recently being studied in schizophrenia, as previously time-domain(TD-OCT) was not able to captures these layers

(Lizano et al., 2020) Decreases in GCL+ can be associated with synaptic loss and neuronal atrophy (Lizano et al., 2020).

Though not commonly explored, a few studies have explored changes of the outer nuclear layer(ONL) and outer plexiform layer(OPL) in schizophrenia. The ONL has rods and cone cell bodies and their nuclei, whereas the OPL is a synaptic layer containing the synaptic process of rod and cone cells, bipolar cells and horizontal cells. Studies have shown that the OPL and ONL are known to behave in a counteracting manner (Bannai et al., 2020). In a previous study performed by Bannai et al., 2020 it was found that a decrease in the ONL thickness was associated with a reduction in overall cognition and greater OPL thickness was differentially associated with fewer positive symptoms of psychosis and poorer overall cognitive performance (Bannai et al., 2020). Additionally, another study performed by Samani et al., 2018) showed that ONL thickness was negatively correlated with an increase in Positive and Negative Symptom Scale(PANSS)negative symptoms.

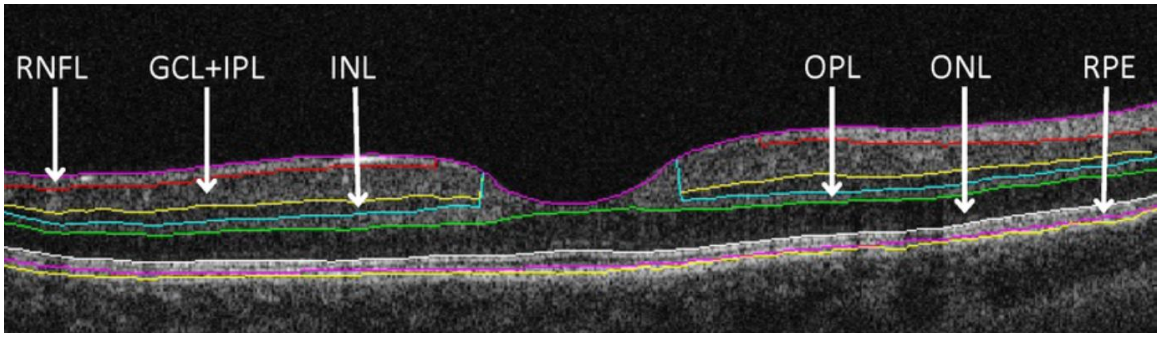
OCT

Optical coherence tomography (OCT) is a non-invasive retinal imaging technique that generates high resolution cross-sectional images of the human eye. An important feature of OCT is that it is a non-contact imaging technique (Aumann et al., 2019). OCT works by using light waves instead of sounds waves like ultrasound machines to gather high resolution cross section retinal images seen in figure 4. OCT machines work by taking a non-invasive scan of both eyes. In figure 4 an example of an OCT machine is present. Each OCT machine has its own unique automatic algorithm which is calibrated by the

manufacturer that is used to delineate different layer of the eye along with giving thickness measures as seen in figure 4, and additionally to complete each scan takes less than a minute. The automatic segmentations were assessed for proper delineation according to the International Nomenclature for Optical Coherence Tomography Panel (Staurenghi et al., 2014) and manually edited to fix any improper delineations.

Figure 4: OCT Scan Setup. An example of how OCT measurements are gathered for participants. The participant put his head on the chin rest and the technician will take picture of both eyes, which will be analyzed thru different automatic algorithms to get different OCT layer thickness (*OCT - Stephen Beswetherick Opticians*, n.d.)

Figure 5: Macular OCT Segmentation Image. This is a figure of the delineation of retinal layers which are labeled. This is done by the automatic algorithm that is present for each OCT scanner (Debuc, 2015).



The time-domain OCT was the first commercial OCT hardware that was used for retinal imaging (Gabriele et al., 2011). A downside to TD-OCT was that it had a slow imaging speed and low axial resolution which resulted in a poor image quality. Since the creation of TD-OCT there has been two different improvements. These are better axial resolution and scanning speed, which was available through in the spectral domain-OCT (SD-OCT), and swept source-OCT (SS-OCT). The creation and use of SS-OCT came to the market after SD-OCT. Compared to the original TD-OCT, SD- OCT and SS-OCT use a broadband light source and no moving reference mirror is required. Also, in SD-OCT and SS-OCT, eye motion artifacts are greatly reduced. Compared to SD-OCT, SS-OCT has a narrow band light source which is swept through a broad range, and it has a higher scanning speed than SD-OCT (Gabriele et al., 2011). Currently, most studies analyzing structural changes in the retina in schizophrenia have used peripapillary OCT measurements (Lizano et al., 2020).

OCT scanners are used by ophthalmologist to diagnose retinal diseases such as glaucoma, age related macular degenerations, and diabetic retinopathy. OCT measurement can detect small changes in retinal layers, which can affect visual processing. Additionally, since changes in retinal layer morphology have been associated with cortical changes in various neuropsychiatric disorders such as multiple sclerosis (Saidha et al., 2011) , Alzheimer's disease (Berisha et al., 2007; Parisi et al., 2001) and schizophrenia (Bannai et al., 2020; Lizano et al., 2020), OCT is being used as a proxy marker for brain changes.

However, due to the presence of different models of OCT scanners, studies have compared the reliability of inter-scanner and intra-scanner measurements of retinal layers on different OCT scanners. Inter-scanner measurements are analyzing the measurements between two different scanners, whereas intra-scanner measurements are comparing the measurements within each scanner that is being analyzed. These differences in measurements may be due to OCT device, technology (time domain, spectral domain, or swept source), imaging parameters, auto-segmentation software, and patient cooperation (Hong et al., 2019). To compare scanner reliability, interclass correlation coefficient are used. The closer the value is to 1, the greater the agreement. The studies examining OCT scanner reliability have been primarily conducted in healthy controls (Pierro et al., 2010, 2012) or in individuals with ophthalmologic diseases such as glaucoma (Lee et al., 2016). A study by Hong et al., 2019 compared the reliability between Triton Topcon swept source-OCT (SS-OCT) and Topcon spectral domain OCT (SD-OCT) devices in healthy controls and those with retinal diseases ranging from age-related macular degeneration, diabetic

retinopathy, retinal vein occlusion, epiretinal membrane and central serous chorioretinopathy, and they found that both OCT devices had excellent intra-scanner agreement of macular RNFL, GCL+ and total retinal thickness measures (Hong et al., 2019). In addition, Miller et al., 2020 examined the reliability of two different SD-OCT scanners in schizophrenia. They found excellent relative agreement with intraclass correlation (ICC) values ranging from 0.85 to 0.99, but poor absolute agreement with ICC values ranging from 0.08 to 0.87 between Cirrus and Heidelberg SD-OCT devices. The Heidelberg SD-OCT demonstrated larger RNFL thickness measures compared to the Cirrus SD-OCT. However, there are currently no studies that have explored inter-scanner reliability between SD-OCT and SS-OCT in schizophrenia.

Due to variability present in different OCT scanners, we aimed to test the inter-scanner agreement between Spectralis Heidelberg SD-OCT and Triton Topcon SS-OCT. We also analyzed, the intra-scanner agreement for macular SD-OCT measurements, Additionally we analyzed peripapillary and macular SS-OCT to see if there were group differences between healthy controls and schizophrenia patients. We also tested whether there were any correlations between macular SS-OCT and SD-OCT measurements and clinical and cognitive measures. Finally, we tested whether correlations existed between baseline ONL and OPL measurements and longitudinal clinical and cognitive changes. We hypothesize that there would be low inter-scanner (SD-OCT vs. SS-OCT) and high intra-scanner (OS vs. OD) ICC in both individuals with schizophrenia and healthy controls. We further predict that macular and peripapillary thickness measures will be lower in

schizophrenia and that these thickness reductions will correlate with poorer cognition and worse psychosis symptoms. We additionally predict that there would be a significant correlation between longitudinal cognitive changes and baseline ONL OCT measurements.

SPECIFIC AIMS

1. To use interclass correlation to compare the reliability of spectral domain OCT and swept source OCT macular OCT measurements in sample consisting of healthy controls and individuals with schizophrenia.
2. To determine intra-scanner reliability between macular and peripapillary SS-OCT measurements, macular SD-OCT measurements, peripapillary SS-OCT measurements, and macular SS-OCT measurements
3. To examine group differences between healthy controls and individuals with schizophrenia for peripapillary and macular SS-OCT measurements.
4. To evaluate whether cognition and symptom severity is correlated with retinal thickness changes in HCs and individuals with schizophrenia.
5. To analyze changes in longitudinal clinical and cognition measures after a 6 month follow up when compared to baseline OCT measurement in schizophrenia.

METHODS AND MATERIALS

Participants:

In this nested pilot study, participants were recruited from the Boston site of the Bipolar and Schizophrenia Network on Intermediate Phenotype-2 (B-SNIP2) and the Stability of Biotypes: A Longitudinal Evaluation (STABLE) study. The goal of STABLE is to broaden and refine the neurobiologically defined biotype definitions that were created during BSNIP-1 and replicated in BSNIP-2 through the collection of longitudinal measures. Institutional review board approval was obtained in accordance with The Code of Ethics of the World Medical Association (Declaration of Helinski). All participants were fluent in English. They additionally had to be able to give informed consent. Probands had a Diagnostic and Statistical Manual of Mental Disorders 4th edition diagnosis (DSM-IV: American Psychiatric Association, 2000) of schizophrenia or schizoaffective disorder.

Healthy controls were excluded if they had a personal history of psychotic or major mood disorder (Structural Clinical Interview DSM-IV-Non-patient edition), family history of psychosis, or schizophrenia-spectrum diagnoses. Participants were excluded in the study if they had (1) substance dependence of abuse within the past 6 months, (2) glaucoma, macular degeneration, retinal occlusions, ocular trauma, or myopia> 4.0 diopters, (3) current pregnancy/breastfeeding, (4) head injury with neurological sequelae, (5) intellectual disability, and (6) neurologic disorders.

Information on clinical and demographic measures were collected as part of the interview. Subjects were screened for cardiovascular or metabolic illnesses such as coronary artery disease, hypertension, diabetes, hyperlipidemia, obesity, and related disorders and assigned a cardiometabolic disease status. Blood pressure was collected in addition to height and weight, which were used to calculate body mass index (BMI). The Fägerstrom Test for Nicotine Dependence was used to determine if the participant had smoked within the past 30 days (Heatherton et al., 1991). Birchwood Social Functioning Scale (SFS), Global Assessment of Functioning (GAF) and the Brief Assessment of Cognition in Schizophrenia (BACS) was used to evaluate all participants for cognition and functioning (Aas, 2010; Birchwood et al., 1990; Keefe et al., 2004). Cognition and functioning tests were performed for all subjects in the sample. SFS is a 79 questionnaire to analyze the social functioning of an individual (Birchwood et al., 1990). Whereas GAF is used measure the daily functional skills and abilities of an individual (Aas, 2010). Lastly BACS evaluates cognitive measures such as verbal fluency, verbal memory, and motor function (Birchwood et al., 1990).

In probands, age of onset of psychosis, illness duration, antipsychotic status, and chlorpromazine (CPZ) equivalents data were collected. Positive and Negative Syndrome Scale (PANSS), Montgomery-Asberg Depression Rating Scale (MADRS), and Young Mania Rating Scale (YMRS) (Keefe et al., 2004; Sajatovic et al., 2015; Young et al., 1978) were assessed for all schizophrenia individuals. MADRS is a ten-question questionnaire to measure the severity of depression (Sajatovic et al., 2015). YMRS is a clinical interview

consisting of 11 questions that is used to evaluate the severity of manic states in a patient (Young et al., 1978). PANSS, is another medical scale that is used to analyze the severity of positive, negative, and general symptoms for schizophrenia patients. All clinical measures were gathered by an experienced clinician. No follow up OCT measurements were collected for the STABLE study, with only clinical and cognitive measures collected at 6 months follow up.

Optical Coherence Tomography

Best-corrected visual acuity (BCVA) was measured using Snellen eye chart using the metric notation. If image capturing was difficult, pupil dilation was performed. All participants underwent retinal imaging using the Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) and Topcon Triton SS-OCT (Topcon, Japan) at Massachusetts Eye and Ear Institute. Macular thickness measures were extracted using both instruments, whereas peripapillary measures were collected only from the Topcon SS-OCT device.

The Spectralis SD-OCT utilizes a scan rate of 40 kHz, scan depth of 1.8 mm, 7 μm axial resolution (3.5 μm/pixel), 14 μm lateral resolution. Additionally, the Heidelberg SD-OCT had a scanning speed of 40,000 and an 870 nm wavelength light source for macular OCT measurements (Puzyeyeva et al., 2011; Verner-Cole et al., 2014). From the Heidelberg SD-OCT, structural measures were obtained for total retinal thickness and for eight retinal layers: RNFL, GCL, IPL, inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigmented epithelium (RPE). This data was

collected by an experienced investigator (Megan Kasetty) using the Heidelberg Spectralis built-in software, Heidelberg Eye Explorer version 1.1.10.0. The automatic segmentations were assessed for proper delineation according to the International Nomenclature for Optical Coherence Tomography Panel (Staurenghi et al., 2014) and manually edited to fix any improper delineations. Early Treatment Diabetic Retinopathy Study (ETDRS) grid was then used to generate a thickness map centered at the fovea which consisted 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) (Figure 6). Thickness measures for each of these nine ETDRS grid sectors were collected for the overall retina and for each retinal layer. The retinal layers data were summed to give GCL+ (GCL and IPL complex) and GCL++ (RNFL, GCL, and IPL complex) measures, to match and compare the data provided by the Topcon SS-OCT device. Furthermore, overall retinal layer thickness was calculated by averaging the weighted mean of each of ETDRS grid sector for both eyes (Figure 6). Spectralis Heidelberg macular OCT measurements of the ONL and OPL were used to observe if any correlations exist between baseline OCT measurements and longitudinal clinical and cognitive measures.

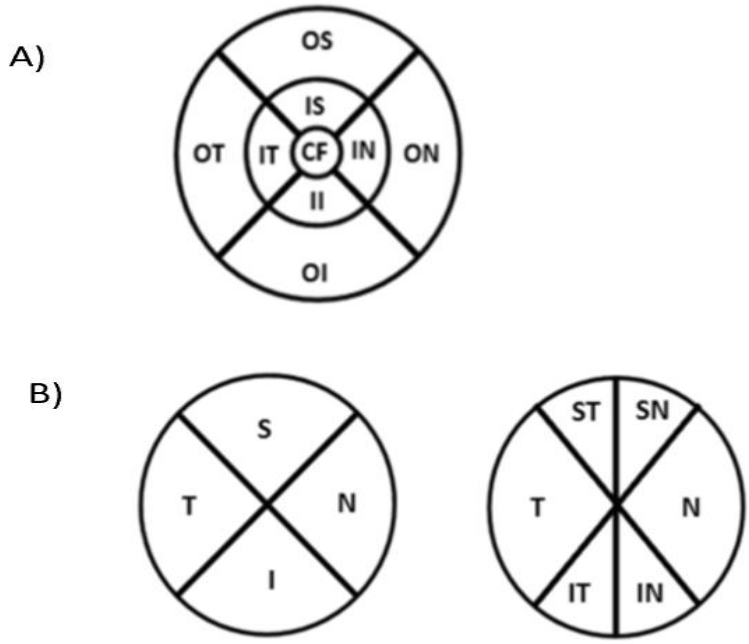


Figure 6: Early Treatment Diabetic Retinopathy Study Grids. A) Grid layout for macular SS-OCT and SD-OCT measurements which were taken at the fovea. B) Grid layout for peripapillary SS-OCT measurements.

The Triton SS-OCT device used a 1,050 nm wavelength light source and scanning speed of 100,000 Angstroms /second. The Topcon SS-OCT gave structural measures for the total retinal, RNFL, GCL+ and GCL++ regions. Using the ImageNet6 software, two experienced raters (Inyia Adhan and Deepthi Bannai) checked the automatic segmentations and manually adjusted those that were improperly delineated. For macular measures, an ETDRS grid was centered on the fovea, and thickness data was extracted for each of the nine sectors. For peripapillary data, an RNFL-6 grid was centered on the optic disk, and thickness measures were extracted for each of the six sectors: superior nasal, superior

temporal, temporal, inferior temporal, inferior nasal, and nasal. Overall retinal layer thickness was calculated by a weighted mean of the RNFL-6 grid sectors for both eyes.

Four participants were excluded in the scanner reliability study due to poor image quality/segmentation on the SS-OCT device. The final sample consisted of 22 healthy controls (HCs) and 30 schizophrenia/schizoaffective (schizophrenia) subjects.

Statistical Analysis

All statistical analyses were performed using R statistical software (version 3.5.1). Sociodemographic group differences were calculated using analysis of variance (ANOVA) and chi-square tests. In addition, ANOVA tests were utilized to test moderator effects of age, sex, race, BMI, smoking status, mean visual acuity, antipsychotic status, systolic and diastolic blood pressure, cardiometabolic disease, and average daily CPZ dosage on overall retinal layer thicknesses. Average daily CPZ dosage was calculated by using the Anderson method (Andreasen et al., 2010)

Intraclass correlation coefficient (ICC) was used for inter-scanner and intra-scanner reliability for the overall retinal layer thickness. ICC is a statistic measures that is used to describe how units in the same group are related to each other (Koo & Li, 2016). An example of a situation using interclass correlation coefficients, would be if there was 3 different raters analyzing the anxiety ratings of 20 subjects. All the values of ratings range from1 to 6, ICC values would be used to see how consistent the values are between the three raters if inter-rate agreement is of interest. Additionally, ICC values can be used to

see whether there was agreement within the raters ratings for anxiety and HCs(“Intraclass Correlation Coefficient in R,” n.d.)The closer the ICC to 1, the stronger the degree of similarity between both measures. To calculate the correlation coefficients, the ICC function in the Psych package in R was used. ICC values were calculated for 1) inter-scanner macular (SD-OCT vs SS-OCT) agreement, 2) intra-scanner (OD vs OS) agreement, and 3) inter-region (peripapillary vs macular regions) agreement for the SS-OCT device. When using the Psych package 6 different ICC values are outputted. ICC values are chosen dependent on three different consideration factors, which are the type of model, agreement, and value. An ICC model can either be one way or two way model. In a one-way random effect model each subject is rated by a different set of random raters. The raters are considered as random effects, and this model is seldom used as many studies use the same raters to measure individuals. There are two different types of two-way models. The first is the two-way random effects model, where there are a set of randomly chosen raters and each subject is measured by the same set of raters to test the agreement in measurements. The intra-scanner agreement would be considered a two-random-effects model. That is, the measurements of a single instrument with multiple raters. The second type of two-way model is the two-way mixed effects model where the raters are fixed, and the results only represent the consistency of the specific raters in the experiment with the instruments varying. This model was used to analyze inter-scanner agreement. The type of measurement they can be is either a single measurement or an average of measurements. The two types of agreement that are present are relative or absolute agreement. In this study, ICC values of interest were for absolute and relative agreement of a single

measurement for a two-way model. Therefore, ICC2 was used for absolute agreement, and ICC3 was used for relative agreement. ICC2 and ICC3 are different outputs that are present when the ICC function is run in the psych package. ICC2 is used for a two-way model analyzing the absolute agreement, whereas ICC3 is used to analyze the relative agreement. The difference between absolute and relative agreement, is that relative agreement deals with the consistency between two or more raters whereas absolute deals with agreement within in one rater's measures. ICC values were categorized as follows; poor (<0.50), moderate (0.50-0.74), good (0.75-0.90), and excellent (>0.90) (Koo & Li, 2016). Negative ICC values indicate that the true ICC value is poor (Taylor, 2010).

For all retinal measurements, a general linear hypothesis test was performed to compare retinal thickness between HC and schizophrenia subjects while controlling for age and BMI. Age and BMI were used as they are a significant moderator of retinal thickness. Partial Spearman correlations were run between macular or peripapillary Triton OCT data and clinical measures as some of the clinical measures were not normally distributed (*Partial.Spearman Function - RDocumentation*, n.d.). Age, sex, and race were used as covariates for clinical and cognitive measures, except for lifetime duration of illness which was covaried for race and sex only. A significance level of 0.05 was set for a 2-sided alternative hypothesis test.

Partial Spearman correlation was run between baseline OCT measurements for OPL and ONL using SD-OCT measurements and percent change in clinical and cognition measures between baseline and follow up measure. The clinical measures of interest were

PANSS total, PANSS positive, PANSS negative, PANSS general and GAF scores. For cognition measures BACS was used. Percent change in clinical measures is calculated by taking the difference between follow up scores collected as part of STABLE from baseline measures part of BSNIP-2 divided by baseline scores. Age, race, sex, and BMI were used as covariates for all retinal measurements. No covariates were used for percent change measures because of the within subject design. A significance level of 0.05 was set for 2-sided alternative hypothesis test.

RESULTS

Demographics

A total of 52 participants (22 HC and 30 schizophrenia) were included in the inter-scanner reliability study. Demographic data is shown in Table 1. In the Topcon SS-OCT data, four participants were dropped due to poor image quality and segmentation. The schizophrenia and HC groups were matched for age, sex, race, mean visual acuity, cardiometabolic disease, and systolic/diastolic blood pressure, as there was no significant difference between these baseline variables between the two diagnostic groups. P-values less than 0.05 indicated that there was a significant difference between the HC and probands. Smoking status differed significantly between diagnostic groups *(F=5.72, p=0.02)*, with the schizophrenia group having 9 smokers and the HC having none. In addition, probands demonstrated significantly higher BMI measures compared to HC (F=6.67, p=0.01). The schizophrenia group had significantly lower SFS (F=25.40, p=<0.001), and BACS composite (F=7.25, p=0.01) scores compared to HC.

Table 1: Clinical and Demographics Table of Study 1 Sample. The mean, standard deviation, chi-squared and p-value are defined for all variables. Some of the clinical assessments only pertained to schizophrenia, and they did not have chi-squared values or p-values calculated.

	Healthy Controls n=22	Schizophrenia n=30	Chi squared/ F-statistic	P-value
Age: mean (SD)	37.4 (11.5)	36.2 (12.7)	0.12	0.73
Sex (F/M)	7/15	9/21	0.00	1.00
Race (AA/CA/OT)	3/15/4	10/15/5	2.71	0.26
Smoking (No/Yes)	21/0	21/9	5.72	**0.02**
Cardiometabolic Disease (No/Yes)	15/6	21/9	0.00	1.00
Best Corrected Visual Acuity	0.94 (0.25)	0.82 (0.30)	2.44	0.13
BMI: mean (SD)	26.3 (3.9)	30.9 (7.9)	6.67	**0.01**
Systolic BP: mean, (SD)	122.1 (9.7)	124.9 (15.7)	0.47	0.50
Diastolic BP: mean (SD)	77.3 (10.1)	75.9 (13.5)	0.14	0.71
SFS Total: mean (SD)	153.2 (16.6)	126.6 (19.8)	25.4	**<0.001**
BACS composite: mean (SD)	-0.07 (0.81)	-0.68 (0.75)	7.25	**0.01**
GAF composite: mean (SD)	82.0(9.1)	45.5(14.9)	99.8	**<0.001**
PANSS Total	--	55.8 (14.3)	--	--
PANSS Negative	--	13.9 (4.8)	--	--
PANSS Positive	--	13.1 (4.6)	--	--
YMRS	--	0.96 (0.64)	--	--
MADRS	--	12.5(9.4)	--	--
Duration of Illness (months)	--	149.9 (148.9)	--	--
Antipsychotic use (No/Yes)	--	4/26	--	--
Total daily CPZ equivalents	--	219.7 (220.6)	--	--

Note: AA = African Americans; CA = Caucasians; OT = Other; BMI = Body Mass Index; BP = blood pressure; SFS = Birchwood Social Functioning Scale; BACS = Brief Assessment of Cognition in Schizophrenia; GAF= Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale; CPZ = Chlorpromazine. **Bold** = $p < 0.05$.

Moderator Effects

Moderator effects were tested to see whether certain factors were associated with retinal layer thickness. For macular SS-OCT measurements, we determined that visual acuity, race, systolic and diastolic blood pressure, CPZ equivalents, cardiometabolic disorder, and BMI were not significantly associated with retinal layer thicknesses (Appendix A). However, age significantly impacted macular GCL+ and GCL++ thickness ($p=0.002$), and therefore was used as a covariate for the partial spearman correlation test. Furthermore, smoking status showed a significant effect on macular RNFL thickness ($p=0.002$). For peripapillary SS-OCT measurements, we found no effects of age, sex, visual acuity, systolic/diastolic blood pressure, cardiometabolic disorder, BMI, and smoking status on retinal layer thicknesses (Appendix B). Race displayed significant differences associated with peripapillary GCL+ ($p=0.03$) and GCL++ thickness ($p=0.04$), indicating that race should be covaried when running the partial spearman correlation test.

Inter-scanner Agreement (SD-OCT vs SS-OCT)

We utilized the macular OCT measures to compare inter-scanner agreement between Heidelberg Spectralis SD-OCT and DRI Triton Topcon SS-OCT (Tables 2 and 3). The same participant was measured between both scanners. Both scanners have different automatic algorithms which measure the thickness of each layer. Research assistants checked all OCT scans to make sure they were proper delineated according to the International Nomenclature for Optical Coherence Tomography Panel (Staurenghi et al., 2014) and manually edited to fix any improper delineations. The purpose of the inter-

scanner agreement is to see how comparable the two different automatic algorithms present in each OCT scanner is. In healthy controls, we observed excellent relative ICC values for bilateral total retinal GCL+, GCL++ thicknesses. For the OS and OD RNFL, HCs demonstrated poor and moderate relative ICCs respectively. Similarly, probands displayed excellent relative ICC measures for bilateral GCL+ and GCL++ thicknesses and good OD total retinal thickness Furthermore, for bilateral RNFL thickness, we observed moderate relative ICC values for the schizophrenia group.

Absolute IC values for inter-scanner agreement ranged from good to excellent for GCL+ and GCL++ thickness in the HC and schizophrenia groups but was poor to moderate for retinal and RNFL thickness (Table 2 and 3). In healthy controls there were excellent absolute ICC values for bilateral GCL+ thickness and good absolute ICC values for bilateral GCL++. However, there were poor ICC values for bilateral total retinal thickness and RNFL thickness. Like HCs, for schizophrenia there was good to excellent absolute ICC values for bilateral GCL+, and GCL++ thickness. However, there was poor ICC values for bilateral total retinal thickness and RNFL thickness.

Table 2: Inter-Scanner Agreement between SS-OCT and SD-OCT - Healthy Controls. Relative and absolute ICC values were calculated to compares OCT measurements between macular SS-OCT and SD-OCT for healthy controls. For each ICC value the 95% CI interval follows. The CI interval has the lower and upper bound values.

Retinal Measurement	n (Participants)	Heidelberg Mean (SD)	Triton Mean (SD)	ICC (Relative) [CI]	ICC (Absolute) [CI]
OD Retinal	20	273.6 (11.9)	305.2 (12.7)	0.96 [0.92,0.98]	0.22[-0.01,0.56]
OS Retinal	20	272.3 (15.3)	304.9 (13.9)	0.92 [0.83,0.96]	0.27 [-0.01,0.62]
OD RNFL	20	29.1 (2.5)	26.1 (2.4)	0.51 [0.18,0.74]	0.30 [-0.06,0.60]
OS RNFL	20	29.2 (3.6)	26.1 (2.1)	0.25 [-0.13,0.57]	0.17[-0.10,0.45]
OD GCL+	20	69.4 (5.8)	69.2 (5.4)	0.98 [0.95,0.99]	0.98 [0.95,0.99]
OS GCL+	20	69.5 (6.6)	69.2 (5.5)	0.99 [0.97,0.99]	0.99 [0.97,0.99]
OD GCL++	20	95.5 (6.9)	98.2 (7.0)	0.92 [0.83,0.96]	0.86 [0.47,0.95]
OS GCL++	20	95.6 (7.6)	98.3 (9.1)	0.90 [0.80,0.95]	0.85 [0.53,0.94]

Note: SD = Standard Deviation; CI = 95 percent confidence interval; ICC = Intraclass Correlation Coefficient; OD = Right Eye; OS = Left Eye; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner Plexiform Layer; GCL++ = RNFL + GCL+. The results are significant if the CI excludes "zero."

Table 3: Inter-Scanner Agreement between SS-OCT and SD-OCT - Probands. Relative and absolute ICC values were calculated to compares OCT measurements between macular SS-OCT and SD-OCT for healthy controls. For each ICC value the 95% CI interval follows. The CI interval has the lower and upper bound values.

Retinal Measurement	n	Heidelberg Mean (SD)	Triton Mean (SD)	ICC (Relative) [CI]	ICC (Absolute) [CI]
OD Retinal	29	269.5 (11.0)	299.3(13.1)	0.81 [0.67,0.90]	0.20 [-0.03,0.50]
OS Retinal	29	268.7 (13.2)	301.4 (11.7)	0.71 [0.51,0.83]	0.16 [-0.03,0.43]
OD RNFL	29	28.4 (2.8)	25.1 (2.6)	0.75 [0.57,0.86]	0.45[-0.06,0.74]
OS RNFL	29	27.5 (3.3)	25.2 (2.5)	0.57 [0.32,0.75]	0.46 [0.11,0.69]
OD GCL+	29	68.2 (4.4)	68.7 (4.4)	0.96 [0.92,0.98]	0.95 [0.91,0.97]
OS GCL+	29	68.4 (5.7)	68.7 (4.9)	0.89 [0.80,0.94]	0.89 [0.80,0.94]
OD GCL++	29	96.4 (6.4)	93.9 (6.4)	0.95 [0.92,0.98]	0.88[0.25,0.96]
OS GCL++	29	95.7 (7.3)	93.9 (6.7)	0.87 [0.77,0.93]	0.86 [0.74,0.92]

Note: SD = Standard Deviation; CI = 95 percent confidence interval; ICC = Intraclass Correlation Coefficient; OD = Right Eye; OS = Left Eye; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner Plexiform Layer; GCL++ = RNFL + GCL+. The results are significant if the CI excludes "zero."

Intra-scanner Agreement (OD vs OS)

To compare intra-scanner agreement, we compared OD and OS retinal structural measures for each device for macular SD-OCT and SS-OCT measurements and peripapillary SS-OCT measurements (Tables 5 and 6). For the macular Heidelberg SD-OCT, HCs demonstrated excellent absolute ICC between both eyes for all retinal layers of interest. We similarly observed excellent absolute ICC values in probands for RNFL GCL+, and GCL++, and moderate absolute ICC for total retinal thickness.

However, macular SS-OCT, ICC agreement was generally lower (poor to excellent) in both HCs and individuals with schizophrenia. HCs demonstrated good to excellent absolute ICC values for total retinal thickness, and GCL++, but poor absolute ICC for RNFL thickness . However, for the schizophrenia, there was moderate absolute ICC values for total retinal and RNFL thickness, and good absolute ICC values for GCL+ and GCL++ thickness .

Peripapillary SS-OCT absolute ICC ranged from moderate to excellent in HCs and schizophrenia (Table 4 and 5). In HCs there was excellent absolute ICC values for total retinal and RNFL thickness, and good absolute ICC values for GCL+ and GCL++. For schizophrenia, there was excellent absolute ICC for total retinal thickness and good absolute ICC for GCL++ and RNFL thickness . Unlike HC's there was moderate absolute ICC values for GCL+.

Table 4: Intra-Scanner Agreement for HCs. Absolute ICC values were collected for intra-scanner agreement comparing right and left eye OCT measurements. All ICC values were provided with a 95% confidence interval. The CI interval has the lower and upper bound values.

	n	OD Mean (SD)	OS Mean (SD)	ICC (absolute) [CI]
Heidelberg Macular SD-OCT				
Retinal	21	306.4 (13.5)	305.9 (14.3)	0.96 [0.92,0.98]
RNFL	21	26.1 (2.1)	26.1 (2.0)	0.91 [0.81,0.85]
GCL+	21	69.9 (6.2)	70.0 (6.9)	0.97 [0.94,0.99]
GCL++	21	96.1 (7.8)	96.1 (7.8)	0.97 [0.94,0.99]
Triton Macular SS-OCT				
Retinal	20	273.6(11.9)	272.3 (15.2)	0.86 [0.73,0.93]
RNFL	20	29.1 (3.6)	29.1 (2.5)	0.39 [0.04,0.67]
GCL+	20	69.2 (6.6)	69.2 (5.3)	0.92 [0.84,0.96]
GCL++	20	98.2 (7.0)	98.3 (9.1)	0.81 [0.63,0.91]
Triton Peripapillary SS-OCT				
Retinal	19	289.2(22.1)	290.7(23.8)	0.97 [0.92,0.98]
RNFL	19	100.2(14.5)	102.4(15.4)	0.92 [0.83,0.97]
GCL+	19	40.2(5.8)	42.2(4.9)	0.78[0.54,0.90]
GCL++	19	139.1(17.8)	144.6(18.9)	0.85 [0.62,0.94]

Note: SD = Standard Deviation; CI = 95 percent confidence interval; ICC = Intraclass Correlation Coefficient; OD = Right Eye; OS = Left Eye; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner Plexiform Layer; GCL++ = RNFL + GCL+. The results are significant if the CI excludes "zero."

Table 5: Intra-Scanner Agreement for Probands. Absolute ICC values were collected for intra-scanner agreement comparing right and left eye OCT measurements. All ICC values were provided with a 95% confidence interval. The CI interval has the lower and upper bound values.

	n	OD Mean (SD)	OS Mean (SD)	ICC (absolute) [CI]
Heidelberg Macular SD-OCT				
Retinal	30	298.8(18.2)	300.8(11.9)	0.72 [0.54,0.84]
RNFL	30	25.1(2.6)	25.1(2.5)	0.92 [0.85,0.95]
GCL+	30	68.7(4.3)	68.7(4.8)	0.95 [0.92,0.97]
GCL++	30	93.8(6.3)	93.9(6.6)	0.96 [0.92,0.98]
Triton Macular SS-OCT				
Retinal	29	269.7(11.0)	268.7 (13.2)	0.74 [0.57,0.84]
RNFL	29	37.5(3.3)	28.4 (2.8)	0.58 [0.34,0.75]
GCL+	29	68.3(4.3)	68.4 (5.6)	0.83 [0.70,0.90]
GCL++	29	95.7(7.1)	96.6 (6.4)	0.82 [0.69,0.90]
Triton Peripapillary SS-OCT				
Retinal	29	283.6(16.1)	286.6(18.2)	0.90 [0.81,0.95]
RNFL	29	97.9(9.9)	100.4(11.0)	0.74[0.56,0.85]
GCL+	29	40.8(5.5)	43.4(4.7)	0.57[0.26,0.75]
GCL++	29	138.7(14.3)	143.8(13.5)	0.77[0.52,0.88]

Note: SD = Standard Deviation; CI = 95 percent confidence interval; ICC = Intraclass Correlation Coefficient; OD = Right Eye; OS = Left Eye; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner Plexiform Layer; GCL++ = RNFL + GCL+. The results are significant if the CI excludes "zero."

Intra-Scanner Agreement (Macular vs Peripapillary)

To compare intra-scanner agreement between macular and peripapillary measures, SS-OCT device data was used (Tables 6 and 7). In HC and schizophrenia there was poor to moderate relative ICC vales for each layer. In HCs, poor relative ICC values were observed for both right and left eye RNFL OCT measurements measures as well as for OD total retinal and OD GCL++ thickness. There were moderate relative ICC values in both right and left eyes for the GCL+, OS GCL++, and OS RNFL thickness in the HC's sample. In the schizophrenia group, there was poor bilateral relative ICC values for total retinal, RNFL and GCL++ thickness. There were moderate ICC values for OD GCL+ and poor ICC values for OS GCL+.

Table 7: Intra-Scanner Agreement in SS-OCT between peripapillary and macular measurements in HCs. Relative ICC values were calculated for all retinal layers. ICC values are all listed with a 95% confidence interval. The CI interval has the lower and upper bound values.

Retinal Measurement	n (Participants)	Macular Mean (SD)	Peripapillary Mean (SD)	ICC (Relative) [CI]
OD Retinal	19	273.9 (10.7)	289.2(22.1)	0.49 [0.14,0.74]
OS Retinal	19	273.7 (14.4)	290.7(23.8)	0.68 [0.40,0.84]
OD RNFL	19	29.1 (2.6)	100.2(14.5)	0.13 [-0.26,0.49]
OS RNFL	19	29.2 (3.7)	102.4(15.4)	0.19 [-0.21,0.53]
OD GCL+	19	69.6 (5.2)	40.2(5.8)	0.57 [0.25,0.78]
OS GCL+	19	69.6 (6.5)	42.2(4.9)	0.62[0.30,0.80]
OD GCL++	19	98.7 (6.9)	139.1(17.8)	0.40 [-0.02,0.67]
OS GCL++	19	98.7 (9.1)	144.5(18.9)	0.53 [0.19,0.76]

Note: SD = Standard Deviation; CI = 95 percent confidence interval; ICC = Intraclass Correlation Coefficient; OD = Right Eye; OS = Left Eye; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner Plexiform Layer; GCL++ = RNFL + GCL+. The results are significant if the CI excludes "zero."

Table 8: Intra-Scanner Agreement in SS-OCT between peripapillary and macular measurements in schizophrenia. Relative ICC values were calculated for all retinal layers. ICC values are all listed with a 95% confidence interval for schizophrenia. The CI interval has the lower and upper bound values.

Retinal Measurement	n (Participants)	Macular Mean (SD)	Peripapillary Mean (SD)	ICC (Relative) [CI]
OD Retinal	36	269.71(10.8)	283.8(15.8)	0.42[0.13,0.64]
OS Retinal	36	268.9 (12.9)	286.9(17.9)	0.33 [0.03,0.57]
OD RNFL	36	28.6 (2.8)	97.9(9.7)	0.23 [-0.08,0.49]
OS RNFL	36	27.8 (3.3)	100.6(10.8)	0.10 [-0.20,0.40]
OD GCL+	36	68.3 (4.6)	40.8(5.4)	0.58[0.34,0.75]
OS GCL+	36	68.4 (5.9)	43.3(4.7)	0.29 [-0.02,0.53]
OD GCL++	36	96.9 (6.6)	138.7(14.1)	0.44 [0.16,0.65]
OSGCL++	36	95.7 (7.6)	143.9(13.3)	0.37 [0.08,0.60]

Note: SD = Standard Deviation; CI = 95 percent confidence interval; ICC = Intraclass Correlation Coefficient; OD = Right Eye; OS = Left Eye; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner Plexiform Layer; GCL++ = RNFL + GCL+. The results are significant if the CI excludes "zero."

Group Comparisons

We analyzed group differences in retinal macular and peripapillary thickness using data from the Topcon SS-OCT. Group differences were analyzed to see if there are significant change in thickness between the healthy controls and schizophrenia. No significant thickness differences were found for macular retinal thickness measures. We did however observe a trending reduction in macular OS RNFL thickness for schizophrenia

compared to HC (d=-0.52, p=0.08). This reduction was consider to be trending as the p-value was greater than 0.05, but less than 0.1. No significant differences were seen for any peripapillary measures (Appendix C). Group comparisons for the SD-OCT device were not reported or calculated as they have previously been described in Bannai et al., 2020.

Correlational Analysis

Associations between clinical variables and SS-OCT retinal measurements were assessed using partial Spearman correlations. Clinical variables included PANSS total score, PANSS positive and negative symptom sub-scores, MADRS, YMRS score, lifetime duration of illness, average CPZ dosage, GAF score, SFS score, and BACS composite score (Table 9, 10, Figure 7, 8). We found a significant association between GAF score and total retinal (r=0.30, p=0.04), RNFL (r=0.31, p=0.04), GCL+ (r=0.30, p=0.04), and GCL++ (r=0.35, p=0.01) thickness. A trend level correlation was seen between macular GCL+ thickness and SFS score (r=0.29, p=0.05). For the peripapillary measures, lower GCL++ thickness was significantly correlated with higher YMRS scores (r=-0.41, p=0.04). In addition, reduced peripapillary total retinal thickness was associated with lower BACS composite score (r=0.36, p=0.02). and GAF scores (r=0.30, p=0.047). We observed a trend level association between GCL+ thickness and PANSS positive scores (r=-0.37, p=0.06). In a post-hoc analysis, we found that reductions in peripapillary total retinal thickness were associated with poorer verbal frequency (r=0.40, p=0.01) and symbol coding (r=0.31, p=0.04) performance. Partial Spearman correlations for the SD-OCT device were not reported since these were previously published in Bannai et al., 2020.

Table 8: Partial Spearman Correlations between Macular SS-OCT Retinal Layers and Clinical, Functioning and Cognitive measures. Partial spearman correlations and significance values for all clinical and cognitive measures. SFS, GAF, and BACS was taken for the entire sample.

	PANSS Total		PANSS Positive		PANSS Negative		MADRS		YMRS		Lifetime Duration		CPZ Equivalents		SFS		GAF		BACS Composite	
	r	**p value**	**r**	**p value**	**r**	**p value**	**r**	**p value**	**r**	**p value**	**r**	**p value**	**r**	**p value**	**r**	**p value**	**r**	**p value**	**r**	**p value**
Total Retinal	-0.03	0.88	-0.03	0.90	-0.19	0.34	-0.11	0.61	-0.01	0.98	0.27	0.19	-0.17	0.39	0.19	0.21	0.30	**0.04**	0.14	0.35
RNFL	0.16	0.42	-0.03	0.87	0.11	0.59	0.26	0.25	-0.26	0.20	-0.004	0.98	0.08	0.70	0.23	0.11	0.31	**0.04**	0.27	0.07
GCL+	-0.01	0.95	-0.13	0.52	-0.17	0.39	-0.09	0.69	-0.11	0.58	0.27	0.18	-0.13	0.53	0.22	0.14	0.30	**0.04**	0.11	0.45
GCL++	0.05	0.80	-0.11	0.57	-0.10	0.64	-0.01	0.98	-0.21	0.29	0.31	0.12	-0.13	0.53	0.29	0.05*	0.35	**0.01**	0.23	0.14

Note: PANSS= Positive and Negative Syndrome Scale; MADRS = Montgomery Asberg Depression Scale; YMRS = Young Mania Rating Scale; CPZ = Chlorpromazine; SFS = Birchwood Social Functioning Scale; GAF = Global Assessment of Function; BACS = Brief Assessment of Cognition in Schizophrenia; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner plexiform layer; GCL++ = RNFL + GCL+. SFS, GAF, and BACS correlations were performed across the whole sample. **Bold** = $p < 0.05$. * = $p < 0.10$.

Figure 7: Significant Correlations between Macular SS-OCT measurements and functioning. Correlations between macular SS-OCT thickness and GAF measures for (A) retinal thickness, (B) RNFL thickness, (C) GCL+ thickness, and (D) GCL++ thickness.

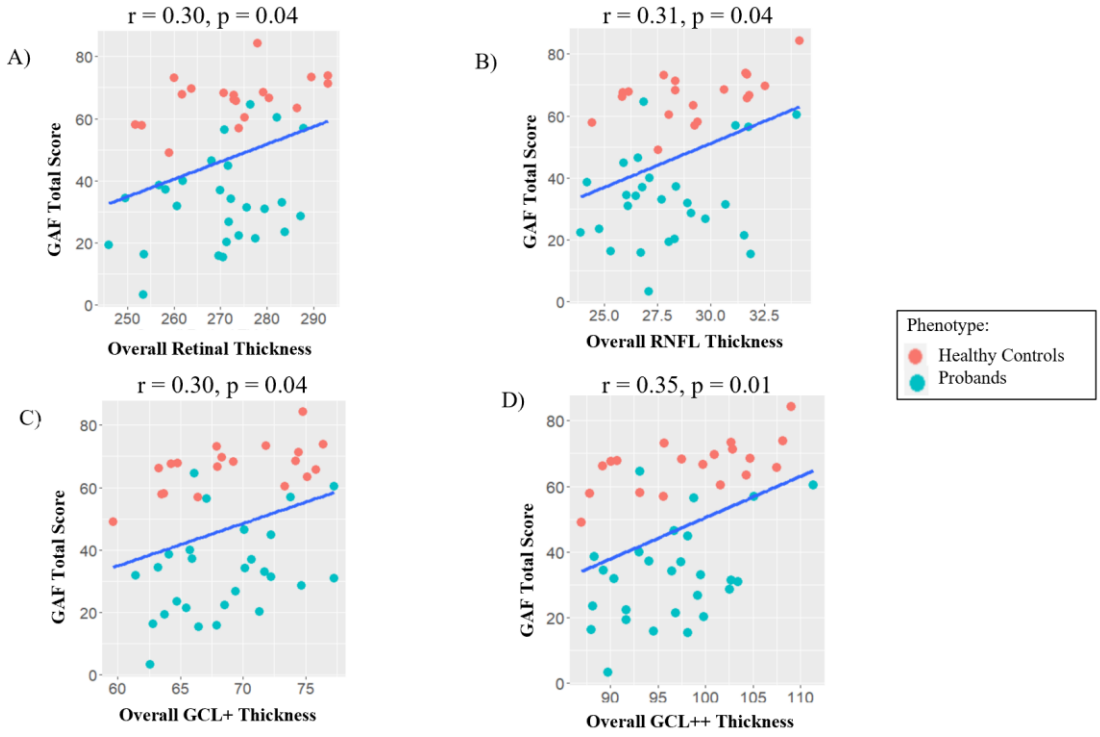


Figure 8: Significant Clinical and Cognitive Correlations for Peripapillary OCT measurements. Correlations between peripapillary SS-OCT thickness and symptom or cognition measures. (A) GCL+ thickness and young mania rating scale total scores, and (B) overall retinal thickness and BACS Composite Scores, C) GAF and overall retinal thickness.

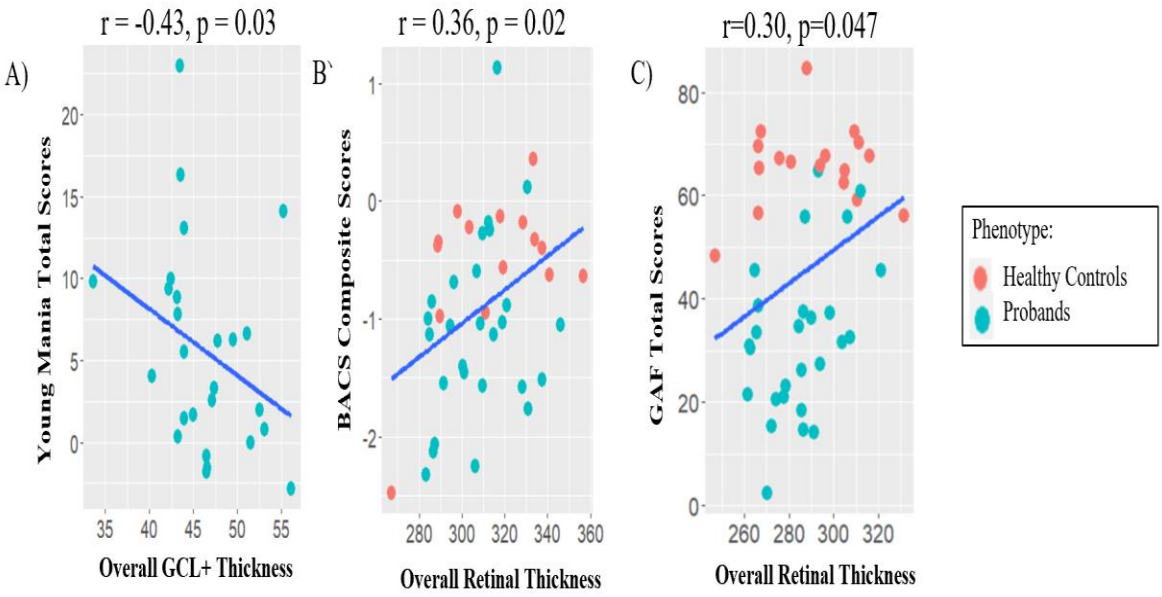


Table 9: **Partial Spearman Correlations between Peripapillary SS-OCT Retinal Layers and Clinical, Functioning and Cognitive measures.** Partial spearman correlations and significance values for all clinical and cognitive measures. SFS, GAF, and BACS was taken for the entire sample.

	PANSS Total		PANSS Positive		PANSS Negative		MADRS		YMRS		Lifetime Duration		Total CPZ Equivalents		SFS		GAF		BACS composite	
	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value	r	p value
Total Retinal	-0.22	0.27	-0.30	0.14	-0.22	0.27	-0.10	0.67	-0.22	0.28	-0.14	0.50	0.01	0.97	0.08	0.56	0.30	**0.047**	0.36	**0.02**
RNFL	-0.09	0.64	-0.22	0.27	-0.20	0.32	-0.06	0.80	-0.09	0.67	0.09	0.68	-0.06	0.80	0.03	0.83	0.16	0.29	0.17	0.29
GCL+	-0.17	0.39	-0.37	0.06*	-0.09	0.66	-0.08	0.73	-0.43	**0.03**	-0.14	0.52	-0.02	0.94	-0.04	0.75	0.17	0.36	0.16	0.29
GCL++	-0.08	0.70	-0.27	0.18	-0.10	0.62	-0.06	0.81	-0.20	0.32	-0.01	0.97	-0.04	0.86	0.008	0.96	0.14	0.28	0.17	0.27

Note: PANSS= Positive and Negative Syndrome Scale; MADRS = Montgomery Asberg Depression Scale; YMRS = Young Mania Rating Scale; CPZ = Chlorpromazine; SFS = Birchwood Social Functioning Scale; GAF = Global Assessment of Function; BACS = Brief Assessment of Cognition in Schizophrenia; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner plexiform layer; GCL++ = RNFL + GCL+. SFS, GAF, and BACS correlations were performed across the whole sample. **Bold** = $p < 0.05$. * = $p < 0.10$.

Longitudinal Analysis

Participants

For the second study, the longitudinal analysis, there were only 7 participants with both retinal imaging data at baseline and clinical data both at baseline and 6-month follow up. All 7 participants have been diagnosed with either schizophrenia or schizoaffective disorder (Table 2). Sociodemographic data can be found in Table 2. All participants are aged from 20 to 55 years old, sample is predominantly male, and all the participants had some college education.

Table 10: Clinical and Demographic Table for Study 2 Sample. Demographic information along with the diagnosis and antipsychotic usage

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Subject 7
Age (years)	20	34	51	46	55	51	43
Sex	Female	Male	Male	Male	Male	Male	Female
Race	Hispanic Descent	African Descent	African Descent	Caucasian	Caucasian	Caucasian	Caucasian
BMI	30.9	33.5	32.4	29.5	29.1	23.8	20.9
Smoking	No	No	Yes	No	Yes	No	No
Education	Some College	Some College	Bachelors	Some College	Some College	Bachelors	Doctorate
Age of Diagnosis for SZ or SAD (years)	17	23	35	32	34	39	42
Age of First Hospitalization (years)	17	21	40	32	37	39	42
Diagnosis	SAD	SAD	SAD	SZ	SZ	SZ	SAD
Antipsychotic	Risperidone 6mg, orally, Daily	Aripiprazole 1mg,orally, Every other day	No medication taken	Aripiprazole 20 mg,orally, Daily	Risperidone Intramuscular every 2 weeks	Olanzapine 1mg, orally, Daily	Quietapine 350mg, orally, Daily Perphenazine 10mg, orally, Daily

Note: BMI=Body Mass Index; SZ= Schizophrenia; SAD=Schizoaffective Disorder.

Analysis

Associations between clinical variables and SD-OCT retinal measurements for ONL and OPL were assessed using partial Spearman correlations. ONL and OPL were used as in previous studies done by the group indicated a significant correlation between ONL reduction and cognition. Clinical variables included PANSS total score, PANSS positive and negative symptom sub-scores, GAF score, and BACS composite score (Table 11, Figure 1). There were no significant correlations between ONL thickness and percent

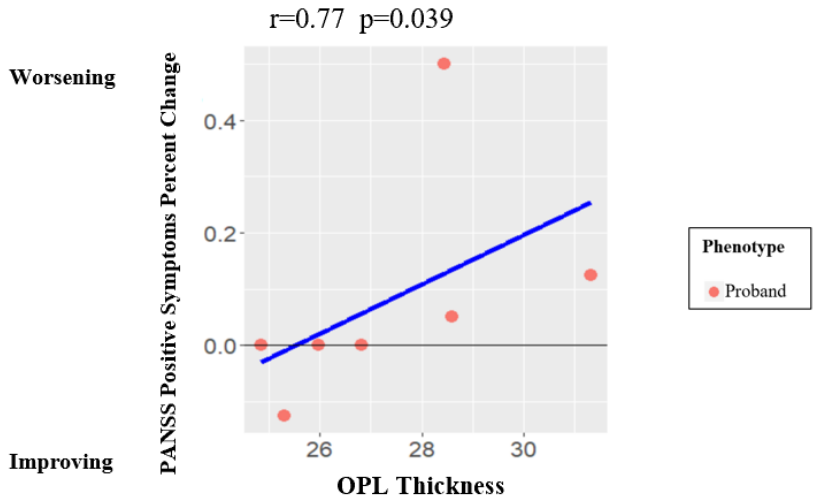
change in clinical and cognitive measures. There was a significant correlation between an increase in the change of PANSS positive symptoms and an increase in OPL thickness (r=0.77, p=0.04). There was a trend level significant correlation with an increase in OPL thickness and change in PANSS total scores (r=0.71, p=0.08).

Table 11: **Partial Spearman Correlations Between Baseline Macular ONL and OPL thickness and Change in Longitudinal Clinical, Functioning and Cognitive Measures.** Partial Spearman Correlations and their significance values. All correlations were run on the entire sample.

	PANSS Total % Change		**PANSS Positive % Change**		**PANSS Negative % Change**		**GAF % Change**		**BACS Composite % Change**	
	r	**p value**	**r**	**p value**	**r**	**p value**	**r**	**p value**	**r**	**p value**
ONL thickness	0.11	0.83	-0.25	0.57	-0.36	0.42	-0.39	0.40	-0.53	0.23
OPL thickness	0.71	0.088*	0.77	**0.039**	-0.22	0.64	-0.29	0.56	0.43	0.35

Note: PANSS= Positive and Negative Syndrome Scale;GAF = Global Assessment of Function; BACS = Brief Assessment of Cognition in Schizophrenia; ONL=Outer Nuclear Layer; OPL= Outer Plexiform Layer. % Change = [follow up - baseline] / baseline * 100; **Bold** = $p < 0.05$. * = $p < 0.10$.

Figure 9: Correlation between OPL Thickness(mm) and Percent Change in PANSS Positive Scores. Negative percent change indicates a reduction of symptoms, and positive percent change indicates an increase of positive symptoms. Percent Change = (follow up-baseline)/baseline



DISCUSSION

To the best of our knowledge, this is the first study to compare retinal layer thickness variability between two generations of OCT scanners (Heidelberg SD-OCT vs. Triton SS-OCT) as well as within-scanner structural differences in a sample containing both HCs and individuals with schizophrenia. This study is also the first to compare baseline outer retinal layer OCT measurements with longitudinal clinical and cognitive measures. We found that bilateral macular retinal measures demonstrated excellent relative and absolute inter-scanner agreement for the GCL+ and GCL++ in both HC and schizophrenia groups. HCs further displayed excellent relative, but poor absolute, inter-scanner agreement for macular total retinal thickness in both eyes. In addition, the macular OS RNFL showed poor relative and absolute ICC values, while macular OD RNFL had a moderate relative ICC and poor absolute ICC values when comparing the measurements between both scanners. In the inter-scanner study, schizophrenia group displayed poor absolute and good relative ICC values for macular OD RNFL, while macular OS RNFL had poor absolute and moderate relative ICC values. These difference in inter-scanner reliability between the right and left eye can be due the variability of OCT measurements between both eyes present in the sample. Additionally, in the intra-scanner study schizophrenia patients also had poor absolute ICC in both eyes for macular RNFL SS-OCT thickness. Macular OD total retinal thickness had good relative ICC and macular OS total retinal had moderate relative ICC values in the schizophrenia group when inter-scanner values were compared. We also found that the intra-scanner agreement for the RNFL, GCL+ and GCL++ thickness was the highest for macular SD-OCT measurements in this study for both healthy controls and

schizophrenia. However, for total retinal thickness, peripapillary SS-OCT measurements had the highest intra-scanner agreement for healthy controls and schizophrenia. Furthermore, macular SS-OCT RNFL measurements had the lowest overall intra-scanner agreement in HC and schizophrenia. Using Triton SS-OCT data, we found that relative intra-scanner agreement between macular and peripapillary retinal layers thicknesses was poor for all retinal layers in both eyes except for OD GCL+ with moderate agreement in HC and schizophrenia groups. Furthermore, we analyzed group differences in peripapillary layer thickness measures and observed no significant group differences between HCs and schizophrenia. Similarly, no significant differences were found in macular layer measures except for a trend level reduction in macular RNFL thickness in schizophrenia compared to HCs. Lastly, macular and peripapillary measures differentially correlated with clinical and cognitive measures. Thinner macular layers were correlated with poorer global functioning and thinner peripapillary findings were correlated with worse YMRS scores and poorer cognitive measures. These findings demonstrate that 1) the GCL+ and GCL++ layers may be more reliable within and between OCT devices, 2) the macular region may be more sensitive to identifying retinal layer differences between cases and controls, 3) while macular measures were sensitive to identifying relationships with global functioning, the peripapillary region had important relationships with cognitive function. Contradictory to our hypothesis we did not find any significant group differences between HC and schizophrenia.

There are currently no studies comparing the inter-scanner agreement between macular GCL+ and GCL++ measurements across Heidelberg SD-OCT and Triton SS-OCT

devices. In a study comparing peripapillary RNFL and GCL+ in healthy subjects between the Cirrus SD-OCT and DRI Topcon SS-OCT, researchers found poor inter-scanner agreement as thickness values varied between OCT scanners (Lee et al., 2016). In studies comparing inter-scanner reliability of peripapillary GCL++ and RFNL thickness between two SD-OCT devices found excellent GCL++ (Matlach et al., 2014) , RNFL, and macular volume agreement (Miller et al., 2020) In addition, Xiong et al. (2020) described excellent inter-scanner agreement in total macular retinal thickness between the Heidelberg SD-OCT and Triton SS-OCT for both controls and patients with diabetes. One reason for identifying excellent relative ICC values for the GCL+ can be due to GCL+ topography being less variable than the optic disc and RNFL (Mwanza et al., 2012). A possible reason for the variation is that the presence of blood vessels around the optic disc that can contribute to structural variation in the RNFL (Yang et al., 2020; Ye et al., 2016). Poor absolute agreement for RNFL and total retinal measurements between the two OCT devices could stem from the use of different automatic segmentation algorithms (Miller et al., 2020; Pierro et al., 2010, 2012). Another potential reason for increased variability in RNFL thickness could be due to the Heidelberg SD-OCT using a 3.46 nm diameter circular scanner around the optic nerve whereas the Triton SS-OCT uses a scanning diameter of 3.40 nm. Since RNFL thickness is greater at the optic disc, the smaller diameter circular scanner used by the Triton SS-OCT could result in a larger RNFL thickness being recorded. In addition, RNFL variability may also be affected by the optic nerve head angle, which affects incidence angle and can lead to some parts of the EDTRS grid to be dimmer (Na et al., 2011; Pierro et al., 2012). Given the growing literature suggesting peripapillary RNFL

thinning in schizophrenia, our findings suggest that comparing RNFL thickness across different OCT scanners should be cautioned (Lizano et al., 2020; Pierro et al., 2012) .

In regard to intra-scanner reliability, Hong et al., 2019 showed that there was a high comparable agreement for macular GCL+, total retinal, and RNFL thickness between SD-OCT and SS-OCT scanners. In HCs, both scanners for peripapillary and macular OCT measurements had good to excellent intra-scanner agreement for total retinal, GCL+ and GCL++ layers as demonstrated by previous studies. The poor RNFL intra-scanner agreement that was observed for macular RNFL could be due to bilateral variability between both eyes. Lastly, scanner agreement of peripapillary RNFL thickness could be impacted by the presence of blood vessels around the optic disc that can contribute to structural variation (Yang et al., 2020; Ye et al., 2016). Intra-scanner agreement was poor for all retinal layers when comparing macular and peripapillary retinal layers in schizophrenia and HCs except for OD GCL+ which had moderate relative ICC agreement. There is currently no known study analyzing intra- or inter-scanner agreement between peripapillary and macular OCT measurements. Poor agreement between macular and peripapillary measures could be due to different retinal thicknesses between the two regions as macular measures are taken at the fovea and peripapillary are taken at the optic disc (Lee et al., 2016).

When analyzing for group differences, we observed no thickness alterations in peripapillary RNFL similar to previous studies (Chu et al., 2012; Silverstein et al., 2018). These results are contradictory to a meta-analysis that observed smaller peripapillary RNFL and GCL-IPL (GCL+) thickness in schizophrenia (Celik et al., 2016; Garcia-Martin

et al., 2019; Lizano et al., 2020). In our study, there were no significant differences in macular thickness measures between HC and schizophrenia groups. For the schizophrenia population, there was trending reduction in macular RNFL thickness, however there was no significant correlation. Though this value was not significant, it was considered to be trending towards significance as the p value was less than 0.1. Previous studies have stated that reductions in macular thickness and volume in schizophrenia could be due to cardiometabolic comorbidities, such as hypertension and diabetes. This did not appear to be the case in the moderator analysis performed in this study which found no relationship between retinal layer thickness and cardiometabolic effects, blood pressure or BMI (Silverstein et al., 2018). A reduction of GCL and IPL volumes has been associated with major depressive disorder (Kalenderoglu et al., 2016), however in our study there was no association between MADRS and thinning of macular or peripapillary retinal layers. Additionally, a lack differences between HC and schizophrenics in the macular and peripapillary regions may indicate that unmyelinated axons remain intact in schizophrenia (Chu et al., 2012). The presence of inflammation due to a recent psychotic episode may also mask the reduction of retinal layer thinning, since inflammatory processes can result in retinal thickness increases (Ascaso et al., 2015; Bannai et al., 2020; Lizano et al., 2020; Silverstein et al., 2018).

The experimental correlation between peripapillary RNFL and GCL+ thickness to symptom severity and illness duration in bipolar disorder and schizophrenia is mixed (Celik et al., 2016; Chu et al., 2012; Garcia-Martin et al., 2019; Lizano et al., 2020; Silverstein et al., 2018). Celik et al., 2016 showed that a decrease in GCL-IPL volumes

was significantly correlated with an increase in symptom severity and illness duration. Furthermore, it was observed that a reduction in the thickness of all macular retinal layers lead to a decrease in global functioning (Celik 2016). However, in a study comparing visual dysfunction in patients with multiple sclerosis it was found that macular ganglion cell complex thinning has more of an effect on visual dysfunction than thinning of the peripapillary RNFL. This indicates that primary retinal neuronal pathology can be more indicative of clinical changes than optic nerve retinal changes (Saidha et al., 2011). Thus, the association between smaller macular thickness and worser GAF scores identified in our study indicate that macula changes can be a proxy for functioning deficits.

There are no studies to our current knowledge that have compared cognition in macular and peripapillary retinal layers in schizophrenia or have analyzed total peripapillary retinal changes in schizophrenia. Studies have identified relationships between smaller peripapillary RNFL thickness and a decline in cognition in Parkinson's disease, mild cognitive impairment and Alzheimer's. This decrease in RNFL thickness is hypothesized to be due to neuronal degeneration of the total retina (Ascaso et al., 2014; Paquet et al., 2007). However, in other studies it has been shown that macular GCL+ is significantly associated with a decline in cognition compared to peripapillary RNFL (Almeida et al., 2019; Sung et al., 2019). Previous studies have mostly used SD-OCT or frequency domain OCT measurement rather than SS-OCT measurements which could lead to mixed results, as each OCT has different light sources, acquisition speed and automatic algorithms. Therefore, comparisons should be made carefully (Almeida et al., 2019).

In this study, there were no longitudinal clinical correlation with baseline macular ONL OCT measurements. This is the first study describing baseline retinal macular deficits in the OPL with longitudinal clinical outcomes in individuals with psychosis. The OPL consists predominantly of a synaptic layer that is located between the photoreceptor cells of the ONL and horizontal, bipolar and Mural cells of the INL. We previously identified larger macular OPL thickness and smaller ONL thickness at baseline in psychosis subjects compared to controls and also found that smaller ONL thickness was significantly correlated with greater OPL thickness (Bannai et al., 2020). In a longitudinal study analyzing changes in macular volume of different retinal layers for early and intermediate age-related macular degeneration, the authors identified OPL expansion and ONL reduction after two years of follow up (Lamin et al., 2019). There are several possible mechanisms that may explain why OPL expansion occurs including, 1) structural compensatory effects by Muller cells, 2) displacement of nuclei from the ONL into the OPL secondary to shrinkage of attached fibers, 3) neuroinflammatory expansion of the OPL due to low resistance to vascular and extra-cellular changes, or 4) measurement error due to the angle of incidence of the OCT beam enhancing Henle's fibers (Bannai et al., 2020; Lamin et al., 2019; Lizano et al., 2020). Cross-sectional implications of retinal deficits on clinical measures have been previously described in psychosis, demonstrating that smaller ONL thickness is associated with worse PANSS negative scores (Samani et al., 2018) and poorer overall cognitive performance (Bannai et al., 2020). In studies comparing the longitudinal effect of schizophrenia it was found that at the end of a 3-year follow up study, it was found that nearly 44.6% of patients who achieved sustained

symptomatic remission had increased cognition especially in verbal, functional and vocational areas (Hui et al., 2012). With stabilization of psychosis, cognition has been noticed to improve which could lead to significant correlation between baseline ONL and OPL OCT measurements.

Limitations

Our study had many strengths, including being the first study to compare retinal layer thickness between SS-OCT and SD-OCT in a sample containing schizophrenia subjects. This was the first study to compare intra-scanner reliability within SS-OCT for macular and peripapillary OCT measurements in a sample of HCs and schizophrenia. Additionally, it was the first to compare baseline OCT measures of the outer retinal layers with longitudinal clinical and cognitive outcomes.

However, our study had limitations as well, such as having a small, heterogeneous sample to compare inter-scanner reliability. The study also included participants with cardiometabolic disorders such as hypertensions and diabetes. In a future study, it could be useful to increase the sample size, and possibly exclude participants with cardiometabolic disorders.

Additionally, the study did not have any peripapillary SD-OCT measures. For the future, it could be good to run both macular and peripapillary SD-OCT and SS-OCT, as having two measures present can be another measure used to compare inter-scanner reliability.

The sample for the longitudinal analysis was a small sample, and only macular baseline OCT measures were analyzed. Considering, that OPL thickness was correlated

with an increase in positive PANSS symptoms, it would be good to increase the sample size to analyze how long term clinical and cognitive changes are correlated to baseline macular OCT measurements. Additionally, it could be useful to see how baseline peripapillary and macular inner retinal measures correlate with longitudinal cognitive and clinical measures, as many previous studies and this study have shown that thinning of the inner retina layers correlate with lower overall cognition, functioning and symptom severity.

CONCLUSION

In conclusion, we found that there is a good to excellent level of inter-scanner consistency for the SS-OCT and SD-OCT for total retinal, GCL+ and GCL++ thickness, with variability present among the measures for RNFL thickness. Between the SS-OCT and SD-OCT macular measurements, we concluded that there was good to excellent intra-scanner correlation among the GCL+ and GCL++ layers, with poor reliability for RNFL measurements. Since there is literature implicating retinal thinning in schizophrenia, variability in RNFL reliability indicates that different OCT scanners cannot be interchanged and that additional precautions should be taken when gathering retinal RNFL OCT measurements. Worse GAF scores was associated with a decrease in macular thickness while a decrease in peripapillary GCL+ was associated with greater mania symptoms, and a decrease in overall peripapillary retinal thickness was associated with worse cognition and GAF scores. Finally, though further research needs to be done, greater OPL thickness may be an indicator of central nervous system changes and a predictor of clinical outcomes in individuals with psychosis.

APPENDIX A

	Total Retinal	RNFL	GCL+	GCL++
Age	0.09	0.09	**0.002**	**0.002**
Sex	0.28	0.21	0.78	0.50
Race	0.93	0.24	0.36	0.20
BMI	0.31	0.90	0.36	0.47
Smoking Status	0.61	**0.02**	0.54	0.13
Best Corrected Visual Activity	0.10	0.31	0.10	0.09
Systolic Blood Pressure	0.19	0.90	0.82	0.84
Diastolic Blood Pressure	0.61	0.59	0.38	0.29
Cardiometabolic Disease	0.41	0.98	0.27	0.38
Daily CPZ Equivalent	0.24	0.63	0.17	0.23
Antipsychotic Use	0.49	0.07	0.65	0.29
Note: BMI = Body Mass Index; CPZ = Chlorpromazine. P-values are presented in the table. **Bold** = $p < 0.05$.				

	Total Retinal	RNFL	GCL+	GCL++
Age	0.09	0.09	**0.002**	**0.002**
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APPENDIX B

Supplementary Table 3a: Group Comparisons between Healthy Controls and Individuals with Schizophrenia using Macular SS-OCT Measurements			
Retinal Measurement	**T-stat**	**Cohen's d**	**P value**
OD Retinal	-1.01	-0.29	0.32
OS Retinal	-0.77	-0.22	0.45
OD RNFL	-1.01	-0.28	0.32
OS RNFL	-1.79	-0.52	**0.08**
OD GCL+	-0.61	-0.17	0.55
OS GCL+	-0.52	-0.15	0.60
OD GCL++	-0.88	-0.25	0.38
OS GCL++	-1.28	-0.37	0.21
Note: OD = Right Eye; OS = Left Eye; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner Plexiform Layer; GCL++ = RNFL + GCL+. **Bold** = $p < 0.1$.			

Supplementary Table 3b: Group Comparisons between Healthy Controls and Individuals with Schizophrenia using Peripapillary SS-OCT Measurements			
Retinal Measurement	**T-stat**	**Cohen's d**	**p value**
OD Retinal	-1.22	-0.34	0.23
OS Retinal	-0.82	-0.23	0.42
OD RNFL	-1.00	-0.26	0.35
OS RNFL	-0.92	-0.28	0.32
OD GCL+	0.06	0.01	0.95
OS GCL+	0.74	0.21	0.46
OD GCL++	-0.54	-0.15	0.59
OS GCL++	-0.53	-0.15	0.60
Note: OD = Right Eye; OS = Left Eye; RNFL = Retinal Nerve Fiber Layer; GCL+ = Ganglion Cell Layer + Inner Plexiform Layer; GCL++ = RNFL + GCL+.			

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