

2023

Is retinal perfusion a proxy biomarker for cerebral perfusion in psychosis?

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BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

**IS RETINAL PERFUSION A PROXY BIOMARKER FOR CEREBRAL
PERFUSION IN PSYCHOSIS?**

by

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B.S., Boston University, 2021

Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

2023

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DEDICATION

I would like to dedicate this work to my parents, James and Cynthia, who have always been a source of love and support while allowing me to pursue my passions.

ACKNOWLEDGMENTS

I would like to thank Dr. Paulo Lizano for all the knowledge, expertise, and guidance that has been provided for me while working on my thesis. Additionally, I would like to thank Chelsea Kiely for all her editing help and feedback and Victor Zeng for assistance in teaching me how to code using R. This paper would never have been accomplished without your support.

Lastly, I would like to thank my classmate and friend, Haley Cox, for all the moral support and encouragement. You were a source of strength for me during this process.

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ABSTRACT

Background: The brain and retina are derived from the neuroectoderm and have structural and functional similarities. Researchers have separately analyzed brain and retinal perfusion in psychosis patients, but few studies have investigated the relationship between them. While the retina can serve as a proxy for brain disorders such as Alzheimer’s or Parkinson’s, less is known for psychosis. Thus, this study aims to examine the connection between retinal and brain perfusion in patients with psychosis.

Methods: A total of 48 participants, 17 healthy control and 31 probands, took part in the Bipolar and Schizophrenia Network on Intermediate Phenotype-2 (BSNIP-2) study at the Boston location at Beth Israel Deaconess Medical Center. Participants underwent arterial spin labeling MRI (magnetic resonance imaging) and retinal OCTA (optical coherence tomography angiography) imaging to determine brain and retinal perfusion, respectively. Whole retinal layer (superficial, deep, and choriocapillaris) and lobe-wise brain perfusion (frontal, temporal, parietal, occipital, and cingulate cortices) was used for analyses. Statistical analysis was performed in R and results were summarized using basic descriptive statistics.

Results: In probands, there was a significant positive correlation between vessel diameter index (VDI) and frontal lobe perfusion ($r=0.74$, $p=0.000027$) and between vessel diameter (VD) and frontal lobe perfusion ($r=0.64$, $p=0.00077$), but not for healthy controls. There was a significant negative correlation between VDI and temporal lobe perfusion ($r=-0.56$, $p=0.0046$), but not for healthy controls. There were no significant results for healthy controls or probands between retinal perfusion and occipital lobe perfusion.

Conclusion: This study demonstrates that retinal perfusion may be a proxy marker for frontal lobe perfusion and could be used for predicting cognitive performance in a psychosis population given that the frontal lobe is primarily involved in executive functioning. There was an absence of a relationship between retinal perfusion and the occipital perfusion which suggests that retinal perfusion does not match visual neuronal pathway connections to the occipital cortex. These findings demonstrate a step towards appreciating how the retina can be leveraged to understand brain dysfunction in psychosis.

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LIST OF ABBREVIATIONS

AD.....	Alzheimer’s Disorder
BACS.....	Brief Assessment of Cognition in Schizophrenia
BBB.....	blood brain barrier
BMEC.....	brain microvascular endothelial cells
BPD.....	Bipolar Disorder
BRB.....	blood retinal barrier
BSNIP-2.....	Bipolar and Schizophrenia Network on Intermediate Phenotype – 2
CBF.....	cerebral blood flow
CNS.....	central nervous system
D-KEFS.....	Delis-Kaplan Executive Function System
DSM-IV.....	Diagnostic and Statistical Manual of Mental Disorders IV
FAZ.....	foveal avascular zone
FD.....	fractal dimension
GCL.....	ganglion cell layer
ICA.....	internal carotid arteries
IPL.....	inner plexiform layer
IQ.....	intelligence quotient
ms.....	milliseconds
OCT.....	Optical Coherence Tomography
OCTA.....	Optical Coherence Tomography Angiography

PANSS.....	Positive and Negative Syndrome Scale
RGC.....	retinal ganglion cell
RNFL.....	retinal nerve fiber layer
SD.....	skeletal density
SFS.....	Birchwood Social Functioning Scale
SZ.....	schizophrenia
VD.....	vessel density
VDI.....	vessel diameter index
WTAR.....	Wechsler Test of Adult Reading
YMRS.....	Young Mania Rating Scale

INTRODUCTION

Psychosis Spectrum Disorders

Psychosis is a psychiatric condition characterized by a variety of symptoms, such as hallucinations and delusions, and spanning several psychiatric disorders, including schizophrenia (SZ), schizoaffective disorder (SZA), and bipolar I disorder (BPD). SZ and SZA groups are combined in research studies since there is a lack of data supporting pathophysiological differences between the two disorders (Mathalon et al., 2010). BPD can be broken down into three categories, bipolar I disorder, bipolar II disorder, and cyclothymic disorder, all of which involve mood, energy, and activity level changes. Patients with bipolar I disorder experience the most extreme changes from manic episodes with psychosis to depression (*Bipolar Disorder*, n.d.). BPD with psychosis is associated with an earlier age of onset, increased number of hospitalizations for mania, and higher education level (Bergen et al., 2019).

SZ is typically diagnosed in early adulthood after a patient displays a combination of positive, negative, and cognitive symptoms. Positive symptoms include hallucinations, delusions, and disorganized speech and behavior (Lewine et al., 1983). Negative symptoms consist of loss of interest and motivation to complete daily activities and lack of interest in socializing (Lewine et al., 1983). Cognitive symptoms are associated with difficulty concentrating and expressing one's thoughts (Arciniegas, 2015). Individuals at higher risk for psychosis development due to a combination of genetic and environmental factors display greater progressive

changes of the brain over time (Fraguas et al., 2016). A meta-analysis conducted by Fusar-Poli et al determined individuals at high risk for psychosis disorders demonstrated impaired neurocognitive functioning and social cognition (Fusar-Poli, Deste, et al., 2012). Across the variety of psychotic disorders, early detection in the prodromal phase and initiation of treatment leads patients to have the best outcomes and least impact to daily life (Schimmelmann et al., 2013).

Medications are available to manage positive symptoms, but negative and cognitive symptoms are not the primary target for antipsychotics treatment (Coyle et al., 2012). Episodes of psychosis are theorized to be caused by an excess of dopamine stimulating D2 receptors. D2 receptors are responsible for regulation of dopamine neurons, synthesis, release, and uptake of dopamine (Ford, 2014). Dopamine has vasoactive effects and can alter cerebral blood flow (CBF) rates (Martens et al., 2021). Antipsychotic medications are theorized to block D2 receptors and thus decrease the intensity and frequency of positive symptoms when patients are compliant with their treatment regime (Coyle et al., 2012). This patient population has a difficult time following a medication schedule and keeping up with appointments for a variety of reasons including medical care access, level of education, and side effects of the medications (García et al., 2016). Additional factors affecting treatment of patients with psychosis are the patient's attitude towards their diagnosis and medications and the degree of cognitive impairment (Martinez-Aran et al., 2009; Molteni et al., 2014). Patients with a positive attitude toward taking antipsychotic medications have

increased adherence, specifically in adolescent populations (Molteni et al., 2014). Patients capable of adhering to a medication regimen and attending follow up appointments have better outcomes (García et al., 2016).

Both genetic and environmental factors increase risk for development of a disorder involving psychosis. Key factors increasing an individual's risk for developing psychosis include family history of psychotic disorder, alterations to normal brain development, genetic mutation on risk alleles, and misuse of alcohol and other drugs (Heckers, 2009). According to a twin study conducted using data from the Danish Twin Register and Danish Psychiatric Research Register (n = 31,524 twin pairs) the heritability estimate is 79% for schizophrenia (Hilker et al., 2018), which is consistent with other twin study results, including a study conducted using data from the Maudsley Twin Register (n = 224 twin pairs, 106 monozygotic, 118 dizygotic) in London, England, estimating heritability at 83% (Cardno et al., 1999). An additional meta-analysis on heritability of schizophrenia using Denmark's population-based registers, the Danish Neonatal Screening Biobank, (Healthy Control n = 871, Cases n = 866) determined risk was strongly associated with family history of psychotic disorders and parental socioeconomic status (Agerbo et al., 2015). In bipolar disorder, individuals with first-degree relatives with a bipolar diagnosis are at a much greater risk of developing the disorder themselves (Rowland & Marwaha, 2018).

Environmental factors from the fetal period, childhood, adolescence, and early adulthood can impact development of a psychosis disorder. In the fetal period, a mother's health and life choices have a direct impact on the fetus (Janoutová et al., 2016). For example, if the mother develops a viral infection there is a chance for the infection to impact fetal development and most specifically brain development (Janoutová et al., 2016; McGrath et al., 2010). Lifestyle choices such as drug and substance use affect psychosis disorder development as well. The most common abused substances in the psychosis population are cannabis, alcohol, and tobacco. Smoking prevalence among individuals with schizophrenia is significantly higher than the general population with about 60% of schizophrenic patients reporting they are current smokers compared to 18% for the general population (Šagud et al., 2009). Numerous studies have shown patients with schizophrenia and a substance use disorder are at increased risk for relapse and hospitalization (Khokhar et al., 2018). Psychosocial stressors, including traumatic events, housing complications, and childhood and emotional abuse or neglect, influence psychosis development as well, specifically for bipolar disorder (Rowland & Marwaha, 2018). When diagnosed patients experience a significant life event, they are at increased risk for relapse of mania or depressive episodes (Kessing et al., 2004).

Diagnosis of psychosis spectrum disorders does not typically occur until early adulthood; however, development of the disorder can start as early as prenatal neurodevelopment. The early neurodevelopmental which occurs in infancy and

childhood is important because the majority of synaptic connections are made, while in adolescence, synaptic pruning, or elimination of extra synapses, occurs (McCutcheon et al., 2019). The process of normal synaptic pruning has been shown to be disrupted in psychosis spectrum disorder patients leading to important portions of synapses to be eliminated (Germann et al., 2021). Imaging studies support the idea of abnormal synaptic pruning with scans depicting increased grey matter loss and irregular network organization manifesting as cognitive deficits in patients (Fusar-Poli, Radua, et al., 2012; McCutcheon et al., 2019). In addition to synaptic pruning abnormalities, psychosis patients display vasculature abnormalities in the brain and retina. When comparing healthy controls to patients, patients displayed alterations in brain perfusion, most notably lower perfusion rates to the frontal lobe (Squarcina et al., 2015). SZ and BPD patients have narrower arteries and wider venules in the retina when compared to healthy controls (Appaji et al., 2019). de Jong et al analyzed the relationship between retinal vessel diameters and cerebral oxygen supply and determined that wider venular diameters was associated with lower arteriolar oxygen saturation to the brain (de Jong et al., 2008).

Psychosis is a complex psychiatric condition with numerous factors affecting onset of disease, symptoms, medication management, and disease progression. Every individual will have a unique experience and combination of disease factors. In addition to clinical and symptom measures to assess psychosis, other measures are

used to examine the effects. We can utilize brain imaging to determine brain structure, function, and perfusion.

Brain Perfusion in Psychosis

Cerebral circulation is responsible for maintenance of brain perfusion and is divided into anterior and posterior circulation with both coming together at the circle of Willis (Figure 1). Anterior circulation consists of the internal carotid arteries (ICA), anterior cerebral artery, and middle cerebral artery, all supplying the frontal, parietal, and temporal lobes (Rosner et al., 2022). The ophthalmic artery is a branch of the ICA and is anatomically closer in proximity to blood supply of the frontal, parietal, and temporal lobes. Posterior circulation consists of the vertebral arteries and supplies the occipital lobe, brainstem, and cerebellum (Rosner et al., 2022).

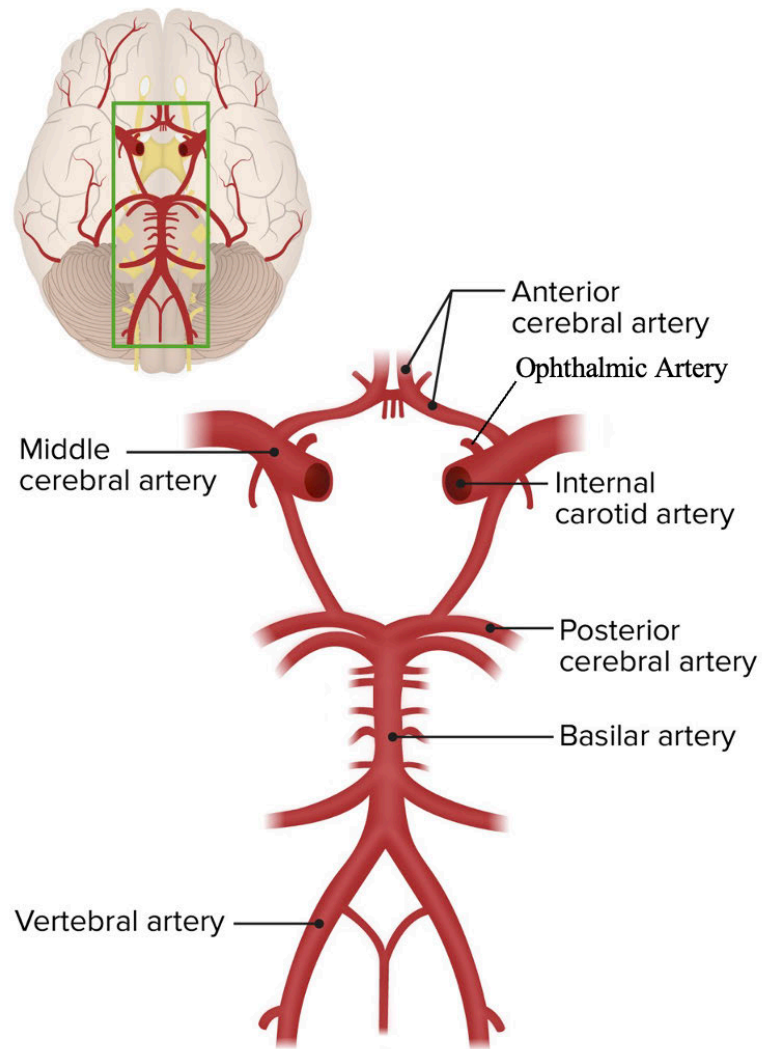


Figure 1: Cerebrovascular system anatomy is divided into anterior and posterior systems which come together at the Circle of Willis (*Cerebrovascular System, 2022*).

The blood brain barrier (BBB) is composed of endothelial cells connected by tight junctions, astrocytes, pericytes, perivascular macrophage, and a basal membrane (Patel & Frey, 2015). Cells of the BBB restrict passage of large and hydrophilic solutes into the brain while allowing for diffusion of small lipophilic molecules, such as oxygen and carbon dioxide (Patel & Frey, 2015). Continual delivery of oxygen and nutrients, such as glucose, occurs at the capillary level and is highly important to neurons in the brain due to their limited ability for carrying out anaerobic metabolism. Capillaries in the brain are non-fenestrated and held together by tight junctions to regulate the movement of ions and molecules from the outside of the body and the brain (Daneman & Prat, 2015). Within this layer of endothelial cells, there are transporters to assist with nutrient and waste transport. Capillaries of circumventricular organs are fenestrated allowing for increased permeability to solutes (Daneman & Prat, 2015).

Brain perfusion data from arterial spin labeling MRI provides information about brain function and activity based on the amount of blood being utilized in each area. Alterations in brain perfusion can lead to ischemic injury and compromise of the BBB (Fantini et al., 2016). A systematic review of 60 studies identified brain perfusion alterations in psychosis, including lower perfusion rates to frontotemporal regions and higher perfusion rates to white matter and the basal ganglia (Mouchlianitis et al., 2016). A study conducted by Fond et al identified right inferior frontal gyrus, an area involved in emotion recognition and connected to the pre-

frontal cortex, perfusion rates to be negatively correlated with persistence of positive symptoms in patients on antipsychotics treatments (Fond et al., 2021). Additional studies have identified similar results showing decreased brain perfusion in schizophrenic patients when compared to healthy controls (Sukumar et al., 2020). Lower CBF values, specifically decreases in CBF to the frontal lobe, have been associated with negative symptoms (Kealy et al., 2020).

BPD patients show brain perfusion changes when compared to healthy controls, including a decrease in CBF to the right temporo-occipital region and greater CBF in the left occipital cortex (Zeng et al., 2021). A study conducted by Dev et al analyzed the relationship between CBF and cognitive performance through use of arterial spin labeling MRI while participants completed the Delis-Kaplan Executive Function System (D-KEFS) color word interference test (Dev et al., 2015). Performance on the D-KEFS color word interference test was directly related to CBF with BPD patients who performed better on the response inhibition task demonstrating greater CBF values, specifically to the anterior cingulate cortex. Healthy controls showed no relationship between task performance and CBF values (Dev et al., 2015).

One hypothesis about the cause of brain perfusion changes leading to cognitive symptoms in SZ and BPD is immune cells crossing the BBB due to BBB leakage caused by increased inflammation as shown in Figure 2 (Patel & Frey, 2015; Pong et al., 2020). Then endothelium of the BBB is involved in neurovascular coupling which is

regulation of local blood flow based on neuronal activity (Kaplan et al., 2020). Alterations to the BBB have potential to cause alterations in neural function which effects CBF (Kaplan et al., 2020). Vascular changes in SZ and BPD are not limited to the BBB and have been identified in small arterial and arteriolar cerebral vessels throughout the brain (Kealy et al., 2020). When schizophrenic patients performed cognitive tasks, there was a delay in cerebral blood flow velocity compared to healthy controls; the delay was found to be directly related to symptom severity (Egger 2021). When patients were administered aripiprazole, an anti-psychotic medication with anti-inflammatory properties, cerebral blood flow to frontal and temporal regions and cognitive performance both increased (Peitl 2021).

Utilizing the available mechanisms to measure brain activity and perfusion, we are still limited in the amount of information we can obtain, since brain imaging is expensive, patients with metallic devices, such as a pacemaker, are excluded from MRI imaging. To further study psychosis, additional sources need to be analyzed, one being the retina given the embryological and functional similarities to the brain.

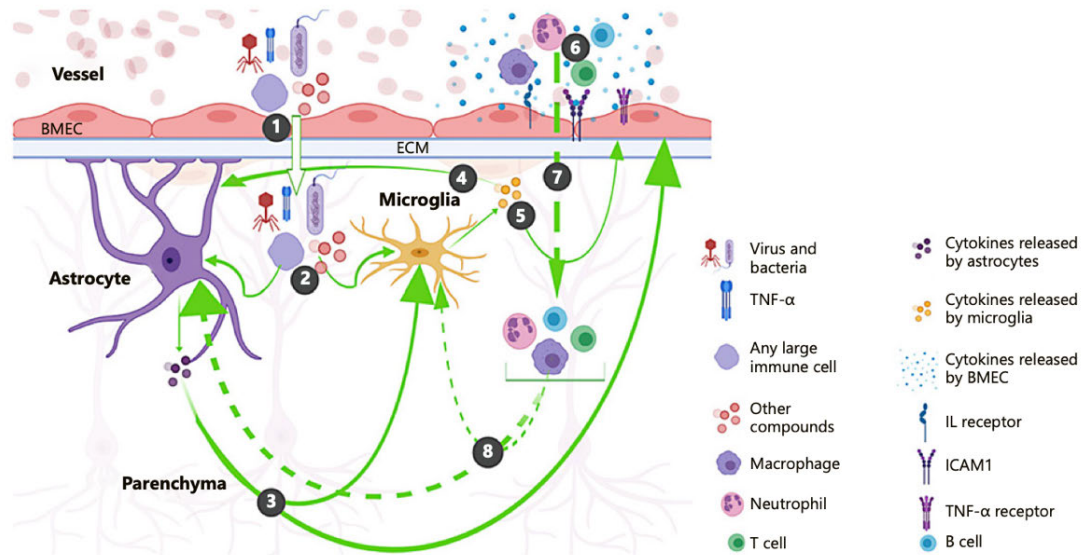


Figure 2: Depiction of the dysfunction of brain microvascular endothelial cells (BMEC) that occurs in schizophrenia. BMECs are a key component of the BBB and lack of structural integrity allows the immune cells to pass through and release inflammatory cytokines as depicted (Pong et al., 2020)

Connection Between Brain and Retina

The brain and the retina work together to carry out numerous processes, such as vision. Both are derived from the same embryonic structure, the neuroectoderm, giving them anatomical and physiological similarities. The brain is protected from the outer environment by the BBB and the retina is protected in a similar manner by the blood retinal barrier (BRB). Both the BBB and BRB are composed of non-fenestrated endothelial cells connected by tight junctions and allow for oxygen and required

nutrients to pass through while preventing passage of additional molecules or ions (Jindal, 2015). Blood flow in the brain and retina is regulated by the BBB and BRB respectively and coupled to neuronal activity to ensure metabolic demands of neurons are met (Nakahara et al., 2013). Pericytes support endothelial cells of the BBB and BRB and in both cases pericytes assist in maintaining blood flow (Patton et al., 2005).

The brain and retina are directly connected via retinal ganglion cell axons of the optic nerve and indirectly connected by retinal and cerebral blood vessels (Figure 3). The retina is thought of as an extension of the brain and is commonly considered a non-invasive diagnostic window into the brain (Appaji et al., 2019). Imaging and monitoring of the retina is carried out by Optical Coherence Tomography (OCT) and OCT Angiography (OCTA) which are fast and non-invasive imaging techniques capable of identifying retinal cytoarchitecture and vasculature at higher resolutions than brain imaging, making the retina a clear choice for further investigation in psychosis (Bannai et al., 2020; Marchesi et al., 2021).

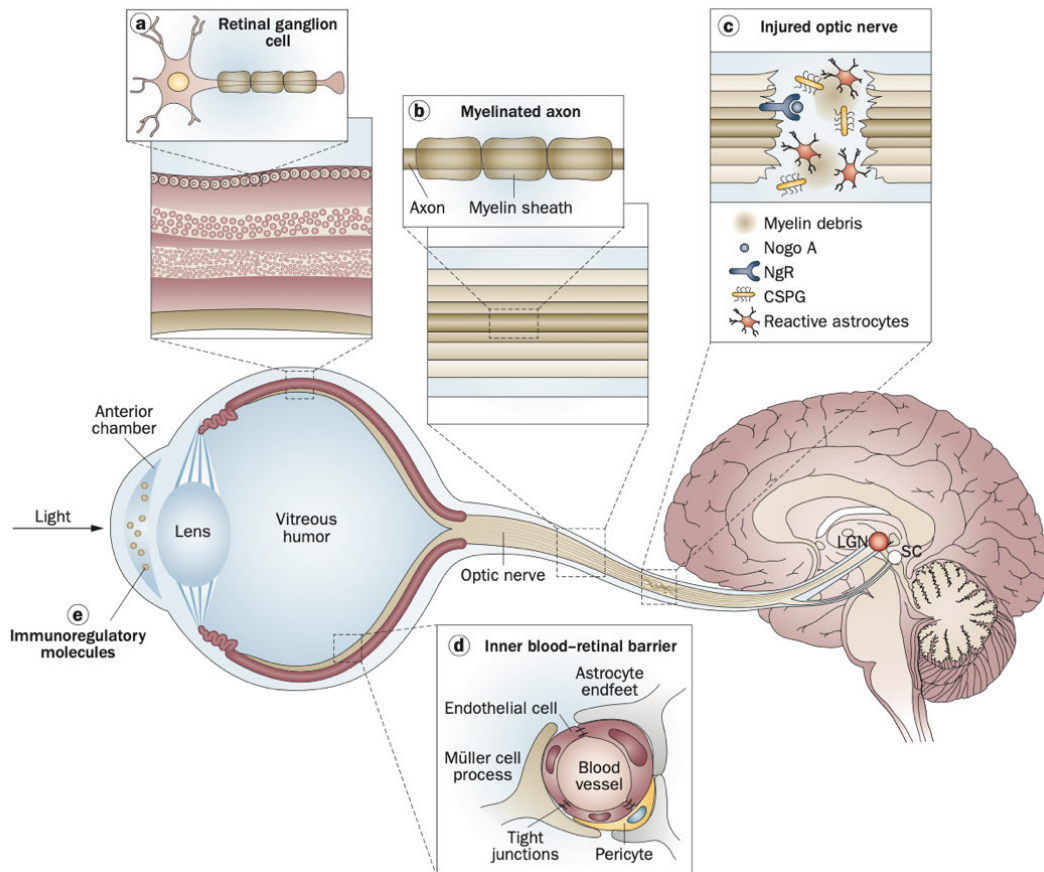


Figure 3: General structure of the retina and connection to the brain. The similarities and connection between the brain and retina are key to utilizing the retina as a window into the brain. (London et al., 2013).

The retina is the inner-most layer of the posterior segment of our eye and lines the entire posterior portion with the exception of the area of the optic nerve. The retinal vasculature system provides oxygen and nutrients to the retinal layers. The

central retinal artery, a branch of the ophthalmic artery, is the blood supply for the inner retinal layers and the choriocapillaris is the blood supply for the retinal pigmented epithelium (RPE) and outer retinal layers (Selvam et al., 2018). The main function the retina is to convert light from the outside world into electrical signals for the brain to interpret as images. The retina accomplishes this with the help of photoreceptor cells, including rods and cones, retinal ganglion cells (RGCs), bipolar cells, horizontal cells, and amacrine cells. Each cell type plays a different role in the conversion of light to electrical signal for the brain. Rods are most abundant in the periphery of the retina and are specialized for light sensitivity. They are “turned on” in darker environments and “turned off” in bright environments. Cones are highly concentrated in the fovea where visual acuity is the greatest and function in color vision with high spatial acuity. Different cone cells are specialized for various wavelengths of light depending on the perceived color (Hoon et al., 2014). Both rod and cones cells will excite their respective bipolar cells before converging onto RGCs; except numerous rod cells will converge onto one RGC whereas one cone cell will converge to one RGC. RGCs receive information from amacrine and bipolar cells before passing the signal along to the optic nerve. Once the electrical signals have reached the optic nerve, they will travel to the optic chiasm where information is sorted. Information from the right and left nasal hemiretina cross to the contralateral optic tract and information from the right and left temporal hemiretina stay uncrossed and travel on the ipsilateral optic tract (Figure 4) (Blind, 2021; Joukal,

2017). Nerve impulses then enter the lateral geniculate nucleus of the thalamus before arriving at the primary visual cortex in the occipital lobe (Mahabadi & Al Khalili, 2022). Any abnormality or injury to the visual pathway will affect the electrical synapse traveling to the brain and will in turn change the information our brain is receiving to form the final visual percept.

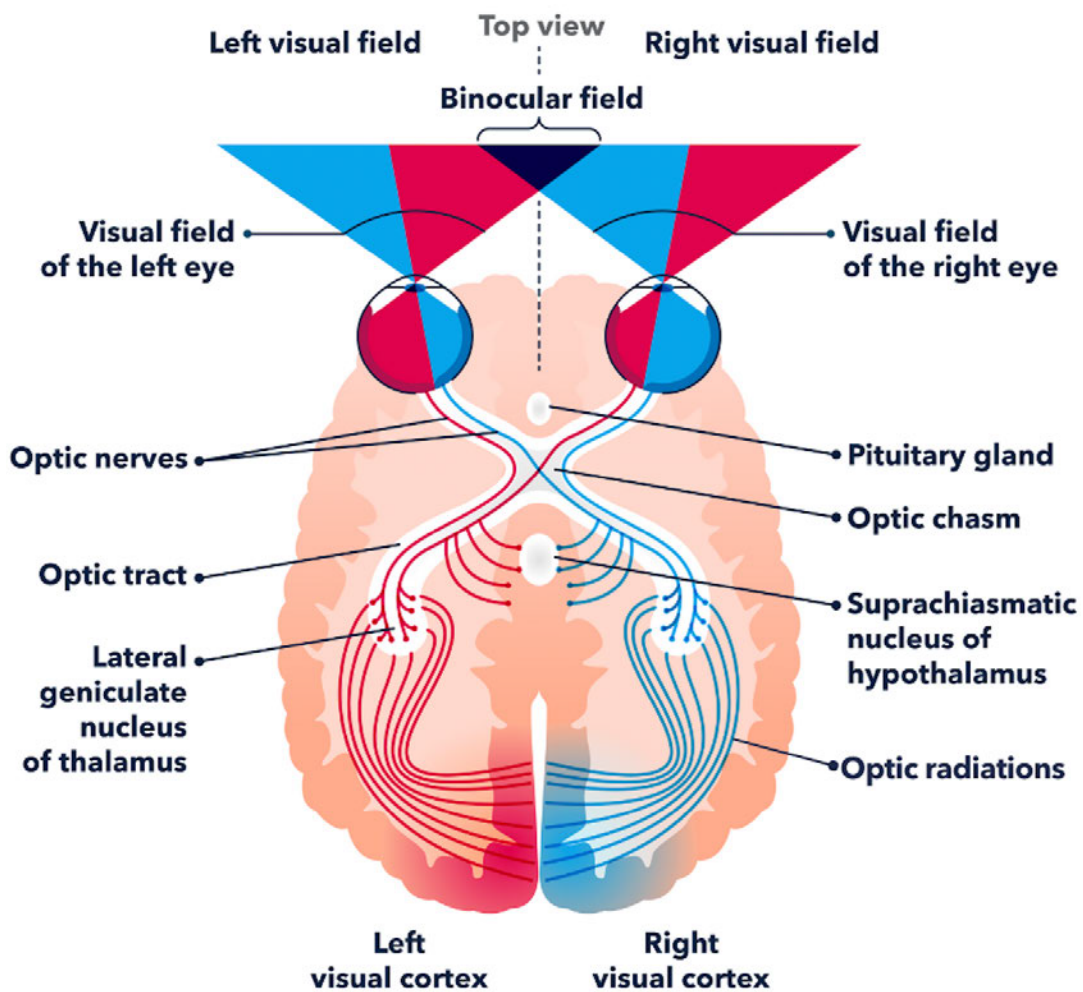


Figure 4: Information flow in the visual pathway (Blind, 2021).

All portions of the visual pathway are important for the brain to construct the final image accurately. The axons of RGCs, which are structurally similar to neurons of the central nervous system (CNS), directly connect the retina and brain through the optic nerve and function in relaying information from the retina to the brain. Structural similarities of CNS neurons and RGCs include both being composed of a cell body, dendrites, and an axon (Jindal, 2015). Degradation of RGCs directly impacts vision leading to irreversible visual field defects due to degradation of the RGCs axon, which make up the optic nerve. Patients with neurodegenerative CNS pathologies often experience visual changes, more specifically decreased visual abilities, and symptoms are often due to direct injury of RGCs or the optic nerve (Marchesi et al., 2021). The similarities and connections between the brain and the retina open a doors for research to identify new diagnostic and/or prognostic biomarkers of brain pathologies.

Retinal Structural Abnormalities in Psychosis

Several studies have analyzed retinal structure changes in patients with psychotic disorders and the potential effects that the structural changes have on symptoms. A systematic review of eleven studies detected thinning of the peripapillary retinal nerve fiber layer (RNFL) in patients with schizophrenia (Kazakos & Karageorgiou, 2020). Hosak's research was able to replicate the finding that patients with schizophrenia had a thinning of the peripapillary RNFL layer, as

well as identify patients to have increased macular thinning and a reduction in overall macular volume. Findings were related to symptom severity and disease duration; patients in a chronic phase of illness displayed more extreme retinal structure changes compared to acute stage and healthy controls (Hosak et al., 2018). Additional retinal abnormalities identified in psychosis disorders include a reduction in volume of the ganglion cell layer (GCL) and internal plexiform layer (IPL) compared to healthy controls (Celik et al., 2016; Lizano et al., 2020). GCL and IPL volumes were lower in treatment refractory patients when compared to treatment responsive patients (Celik et al., 2016). A meta-analysis by Lizano et al (HC n = 904, proband n = 820, SZ n = 541, BPD n = 279) identified similar findings including RNFL and GCL-IPL thinning in SZ and BPD patients (Lizano et al., 2020). Findings highlight the utility of Optical Coherence Tomography (OCT) imaging in monitoring neurodegeneration in psychosis (Celik et al., 2016). OCT technology makes it easy to view the retina *in vivo* and analyze structural changes occurring in neurodegenerative and psychotic disorders.

Importance and Utilization of Retinal Imaging

Improvements in retinal imaging modalities, specifically OCT, has made studying and monitoring the retina more accessible (Almonte et al., 2020). Psychosis spectrum disorders have known cerebral changes; however brain imaging has several limitations leading researchers to look for alternative monitoring methods for

this group of disorders (Lizano et al., 2020). Using OCT technology, retinal thinning, reduced macular thickness, and reduced macular volume have been identified in patients with schizophrenia (Almonte et al., 2020). These retinal changes have been more pronounced in individuals treatment-refractory patients compared with treatment-responsive patients (Almonte et al., 2020). There is potential clinical value for retinal imaging in monitoring pathophysiology of psychosis spectrum disorders and for identification of a diagnostic biomarker (Lizano et al., 2020). Retinal imaging technology has been utilized to monitor and connect retinal changes with cerebral changes in other CNS pathologies, including Alzheimer's Disease (AD) and Parkinson's Disease.

CNS pathologies often have ocular manifestations due to anterograde and retrograde degeneration of the visual pathways (Gupta et al., 2021; Marchesi et al., 2021). Patients with AD or Parkinson's have similar changes to their retinal structure as those seen in psychosis disorders. AD and Parkinson's are the most common illness of the elderly, and both have characteristic neurodegeneration impacting the CNS, which includes the retina. AD is a progressive neurodegenerative disorder mainly thought to affect cognition and memory due to deposits of amyloid-beta plaques. Visual defects, including difficulty with depth perception, reading, and color perception, are early symptoms of AD (Berisha et al., 2007; Jindal, 2015). Previously, symptoms were thought to be associated with degradation of the occipital cortex, however studies on retinal structure have identified significant reduction in RNFL,

specifically in the superior and inferior quadrants, and loss of RGC, which affect the visual capabilities of a patient (Iseri et al., 2006). Retinal structure degradation occurs as AD progresses (Iseri et al., 2006). Patients with more extreme reduction in RNFL layer thickness and RGC loss were identified to have more severe cognitive impairment (Iseri et al., 2006).

Patient's with Parkinson's disease have similar retinal changes to those with AD. Parkinson's disease is a neurodegenerative disorder characterized by loss of dopaminergic neurons largely in the substantia nigra resulting in movement symptoms as well as visual field defects and dementia (Satue et al., 2013). Visual defects experienced by Parkinson's patients, most notably impairments to color vision and reduction in contrast sensitivity, precede motor and additional non-motor symptoms (Müller et al., 2002; Piro et al., 2014). Retinal changes identified in Parkinson's disease include decrease in RNFL thickness and macular thickness (Satue et al., 2013) as well as a reduction in the amount of RGCs (Indrieri et al., 2020). In a longitudinal study on retinal changes in Parkinson's, patients had greater amounts of RNFL thinning compared to controls (Ma et al., 2018). An additional longitudinal study identified RNFL thickness to be associated with cognitive functioning and cognitive decline (Zhang et al., 2020).

Retinal Perfusion Abnormalities in Psychosis

The few studies analyzing retinal perfusion in psychosis identify significant differences between probands and healthy controls. In a study conducted by Bannai et al greater vessel density and skeletal vessel density was identified in probands when compared to healthy controls (Bannai et al., 2022). Reductions in perfusion and vessel density have been identified in the retina of patients with schizophrenia and are associated with the thinning of retinal layers (Silverstein et al., 2021). The decrease in perfusion and vessel density increases ischemia and leads to cell death, all of which have been identified in patients with psychosis (Marchesi et al., 2021; Silverstein et al., 2021). Individuals in the chronic phase of psychosis spectrum disorders demonstrated lower superficial vessel density and higher positive symptoms when compared with individuals in the early course of their disorder (Bannai et al., 2022). Function of microvasculature has been related to scores on the Wechsler Test of Adult Reading (WTAR) which is a method of generating an Intelligence Quotient (IQ) estimate. Patients with more severe changes to microvasculature and perfusion, including wider venule caliber, performed worse on the WTAR assessment and demonstrate lower IQ scores (Shalev et al., 2013).

The connection between retinal structure and perfusion changes to assessment performance and symptoms highlights the importance of further research into the retina and connection to the brain in relation to psychotic disorders. Early intervention and initiation of treatment has an immense impact on the disease

course and overall prognosis of a patient (S.-W. Kim et al., 2020). By analyzing the retinal and cerebral differences in probands compared to healthy controls the hope is to identify a biomarker to be used for early diagnosis and prognostication of clinical outcomes.

Retinal Perfusion Abnormalities in Alzheimer's Disease and Parkinson's Disease

Retinal perfusion abnormalities in Alzheimer's Disease (AD) and Parkinson's have been studied more extensively. AD patients report visual symptoms early in the clinical course and often before pathological changes occur in the brain (Berisha et al., 2007). The developmental, structural, and functional similarities of the brain and retina led researchers to analyze the retinal structure and perfusion in relationship to cerebral changes occurring in AD and Parkinson's. As discussed earlier, studies have come to identify psychosis patients to show similar retinal structural changes. Even so, the literature on retinal perfusion changes and connection between retinal and cerebral changes in psychosis is quite limited.

Neuropathological changes in AD can be identified up to years before clinical symptoms start to show (Hays et al., 2016), specifically researchers have identified changes in cerebral blood flow and vascular dysfunction (Lahme et al., 2018). The long pre-clinical phase can be a potential diagnostic window if a biomarker such as CBF and retinal blood flow can be identified for AD and the disease is caught before symptoms start (Marchesi et al., 2021). In AD, retinal perfusion is reduced and the

lack of oxygen and nutrient delivery subsequently causes death of retinal cells, the majority of cells affected are RGCs (Mancino et al., 2019). The death of RGCs leads to retinal thinning which has been identified in AD and psychosis. Regarding AD, the extent of retinal thinning correlates with the severity of the disease (Garcia-Margin 2016). Reduced retinal perfusion in AD is due to structural abnormalities and amyloid beta deposits within vessels. When amyloid-beta plaques deposit in blood vessels of the brain the retinal vein tortuosity increases, meaning the vessel obstructions in the brain directly affect the blood flow of the retina. The quantity of amyloid-beta deposits in the brain is reflected in the retina. Vascular endothelial growth factor binds to the amyloid-beta plaques and decreases the ability to form new vessels (Bulut et al., 2018). With the decreased blood flow due to plaque deposition and decreased ability to form new vessels, blood flow to the brain and retina is significantly lower in patients compared to healthy controls (Bulut et al., 2018). Findings have been replicated in additional studies, including a study conducted by Berisha and colleagues who identified the diameter of the retinal venous vessels and blood flow rate were markedly decreased compared to healthy controls (Berisha et al., 2007).

Researchers have utilized retinal imaging to examine retinal structure and perfusion abnormalities in Parkinson's Disease with the goal of determining a biomarker for the disease (Zou et al., 2020). Progression of Parkinson's has been associated with small vessel pathology and retinal analysis can enhance

understanding of the pathogenesis of Parkinson's (van der Holst et al., 2015). Cerebral small vessel disease, which has been identified in Parkinson's patients, has been associated with lower retinal fractal dimension (McGrory et al., 2019; Robbins et al., 2021). A cross-sectional study comparing Parkinson's with controls identified lower vessel density and perfusion density in patients (Robbins et al., 2021). Researchers have theorized retinal microvasculature changes associated with perfusion changes, including lower VD and perfusion density, are due to blood vessel regression in Parkinson's (Robbins et al., 2021). An additional study was able to replicate the results above and identified Parkinson's patients to have lower macular VD and lower perfusion densities when compared to healthy controls (Shi et al., 2020; Zhou et al., 2021). Retinal imaging has potential to revolutionize screening practices, clinical management, and monitoring of cellular and molecular events underlying disease progression in CNS pathologies like Parkinson's (Moons & De Groef, 2022).

Specific Aims & Significance

This thesis will investigate the connection between brain perfusion and retinal perfusion in psychosis. As of yet, no study has analyzed the relationship between brain and retinal perfusion in psychotic disorders despite the similarities between the brain and eye and the abnormalities identified in both the brain and retina of patients with psychosis. Researchers have identified a connection between brain and retinal perfusion in relation to other disorders, including Alzheimer's Disease and

Parkinson's, and the perfusion changes are directly correlated with symptom severity and disease progression. Given this, we aim to determine the relationship between brain and retinal perfusion in psychosis and the relationship between perfusion and symptom severity and disease progression.

Aim #1: To investigate the relationship between perfusion of the brain and perfusion of the eye in psychosis.

Hypothesis #1: We predict perfusion of the brain and retina will be decreased in psychosis since psychosis displays similar structural change to other neurological disorders, Alzheimer's and Parkinson's, both of which display decreased brain and retinal perfusion.

Aim #2: To investigate the relationship between retinal perfusion and lobe-wise brain perfusion in psychosis.

Hypothesis #2: We predict perfusion to the frontal and temporal lobe perfusion rates will be altered when compared to health controls due to the anatomical proximity of the ophthalmic artery to the frontal and temporal lobes.

Aim #3: To investigate whether perfusion changes in the eye and brain are related to symptom severity.

Hypothesis #3: We predict decreased perfusion to the eye and brain will be related to greater increase symptom severity and that perfusion changes will be more extreme in patients with increased disease progression. More significant perfusion changes will be seen in patients in chronic stage when compared to early-stage psychosis.

METHODS

Participants

The participants included for this analysis were from the Bipolar and Schizophrenia Network on Intermediate Phenotype-2 (BSNIP-2) study. Participants were from the Beth Israel Deaconess Medical Center site in the BSNIP-2 study. Retinal and brain biomarkers were collected on participants as part of the BSNIP-2 study. All participants were proficient in English and capable of giving written informed consent. Patients with a history of (1) substance dependence or abuse within the past 6 months, (2) glaucoma, macular degeneration, retinal occlusions, ocular trauma or myopia >4.0 diopters, (3) currently pregnant or breastfeeding, (4) head injury with neurological sequelae, (5) intellectual disability, and (6) history of neurologic disorders were not included in the study. Healthy controls were only eligible to participate in the study if they had no personal history of a psychotic or major mood disorder (SCID-nonpatient edition), a family history of psychosis, or SZ-spectrum diagnoses and treatment with medications affecting cognition. Clinical and

demographic information was collected from all participants. Probands in this study carried a diagnosis of SZ, SZA, or BPD based on Diagnostic and Statistical Manual of Mental disorders IV (DSM-IV) and consensus diagnosis. For probands, in addition to demographic and clinical information, information regarding duration of illness and medication status was collected. Symptoms of psychosis were analyzed using the Positive and Negative Syndrome Scale (PANSS) and symptoms for mania were assessed using the Young Mania Rating Scale (YMRS). PANSS is a 30-item clinician-administered rating scale utilized to measure severity of positive and negative of symptoms in psychosis disorders. The core principles of the PANSS assessment include reading each item definition and all anchor points carefully and interpreting each element as literally as possible, assigning the highest rating that applies for each situation, and to always consider the reference period and time frame, which is commonly considered to be the “past week”, and utilize all relevant information for rating (Kay et al., 1987; Opler et al., 2017). The YMRS consists of eleven items and is clinician-administered just like the PANSS assessment. YMRS is utilized to measure severity of mania experienced by patients with psychosis disorders (Kay et al., 1987; Young et al., 1978). Healthy controls (HC) and probands were both evaluated with the Brief Assessment of Cognition in Schizophrenia (BACS) and Birchwood Social Functioning Scale (SFS). The BACS assessment consists six tests focusing on verbal and working memory, motor speed, verbal fluency, reasoning and problem solving, and attention and processing speed to analyzing cognitive function (Richard S. E.

Keefe et al., 2006). The Birchwood SFS is a 79 item self-report of social-functioning consisting of seven subscales: (1) social engagement/withdrawal; (2) interpersonal behavior; (3) prosocial activities; (4) engagement in recreation activities and hobbies; (5) independence-competence; (6) independence-performance; (7) employment. A higher score represents better social functioning (Birchwood et al., 1990; Chan et al., 2019).

Optical Coherence Tomography and Optical Coherence Angiography

Visual acuity was measured using Snellen eye chart in the metric notation. All participants took part in retinal imaging using the Topcon DRI-OCT Triton Swept-Source OCT (Topcon, Japan) which has 100,000 A-scans/s, 4 repeated B-scans, and real-time eye tracking, and uses an innovative OCT-A Ratio Analysis algorithm for image segmentation (Bannai et al., 2022; Ledesma-Gil et al., 2021). Fovea centered 6-x 6-mm² images were extracted from ImageNET 6 (Bannai et al., 2022). A custom semi-automated algorithm with intensity normalization was developed in MATLAB 2018b and utilized to process raw OCT-A images and to extract the following measures: VD, VDI, SD, and FD. Extraction of each of the measures was unique. VD was calculated based on the ratio between the area encompassed by the vessels to the total area of the image. SD was calculated as total amount of white pixels divided by total area of the image. VDI was calculated by dividing VD by SD. FD was calculated by the box-counting method (Bannai et al., 2022). Methodology by Kim et al was

utilized for extraction of microvasculature measurements (Bannai et al., 2022; A. Y. Kim et al., 2016). VD, VDI, SD, FD, and FAZ were utilized to create a whole retinal perfusion measure for both eye, the right eye, and left eye.

Sample size varied for different portions of the analysis. For the foveal avascular zone (FAZ) analysis of the right eye, there was a total of 41 participants, (HC n = 16; Probands n = 25) for the left eye there were a total of 40 participants (HC n = 16; Probands n = 24). The FAZ is a region within the fovea, which is responsible for high-acuity vision and has a high density of cone photoreceptor cells, and at the center of the macula. Analysis of retinal perfusion was based-on vessel density (VD), skeletal density (SD), vessel diameter index (VDI), and fractal dimension (FD) and included a sample size of 48 participants (HC n = 17; Probands n = 31) for the right and left eye. VD quantifies the portion of the retina with detectible perfusion. SD is representative of the length of the retinal vascular network. FD measures the extent of vessel branching and complexity. VDI is the average vessel diameter for the length of retinal vasculature. FD and VDI characterize vessel morphology and SD and VD characterize capillary density (Koulisis et al., 2017). Correlations between retinal perfusion and brain perfusion were also analyzed.

Arterial Spin Labeling MRI

Whole-brain structural three-dimensional magnetic resonance images (MRI) were acquired on two different models of GE 3T scanners including GE Signa HDXT

and MR750. Cerebral blood flow images were processed using the structural, imaging and population module of ExploreASL 1.9.0. For the GE Signa scanner, the repetition times was 1399 milliseconds (ms), echo time 9.8 ms, labeling duration and post labeling delay were both 1500 ms, background suppression was on, the flip angle was 90 degrees, and acquisition duration was 5 minutes:40 seconds. For the MR750 scanner, the repetition times was 4676 milliseconds (ms), echo time 10.5 ms, labeling duration 1450 ms, post labeling delay 1525 ms, the flip angle was 111 degrees, and acquisition duration was 6 minutes:0 seconds. A T1 structural scan according to the ADNI-2 protocol was used for partial volume correction within the ASL preprocessing (Mutsaerts et al., 2020).

Statistical Analysis

All statistical analyses were performed using R software version 2022.07.2 (company). Initially bilateral retinal perfusion and lobe-wise brain measures were analyzed individually using the sample of 48 participants. Measurements utilized to analyze retinal perfusion were obtained from OCTA imaging and include FAZ, VD, SD, VDI, FD. Bilateral FAZ, VD, and VDI measures were then analyzed based layer of the retina for the following layers: superficial, deep and choriocapillaris. FAZ, VD, and VDI measures were further analyzed based on right and left eye. For brain perfusion, lobe-wise perfusion values for the frontal, temporal, parietal, and occipital lobes were utilized to compare healthy controls and probands. After analyzing retinal perfusion

and brain perfusion independently in healthy controls vs probands, these perfusion measures were correlated to determine if there were relationships between the measures. Initial correlations compared whole retinal perfusion vs. whole brain perfusion. Bilateral FAZs, VD, and VDI measures based on layer: superficial, deep, and choriocapillaris were correlated with brain perfusion values before analysis of right and left retinal perfusion to brain perfusion.

Data was summarized using basic descriptive statistics. All p values <0.05 were considered statistically significant. We performed numerous correlation comparisons between retinal and brain perfusion, between retinal perfusion and symptom scale measures, and between brain perfusion and symptoms scale measures. Analysis started with whole perfusion measure for the retina vs. brain perfusion and significant results were hierarchically examined to identify which eye, quadrant or region was more specifically implicated.

Results

Demographics

A subset of participants who participated in the BSNIP-2 study at the Boston site were included in this analysis. Probands and healthy controls were matched for age, sex, and race, best corrected visual acuity, diastolic/systolic blood pressure, and cardiometabolic disease status (Table 1).

Table 1: Demographics Information for Participants

	Healthy Controls (n=17)	Probands (n=31)	P Value (all groups)
Age (mean, SD)	37.882 (11.494)	34.355 (12.142)	0.546
Sex (M/F)	13/4	21/10	0.754
Race (CA/AA/OTH)	9/6/2	17/8/6	0.323
Diagnosis Group (SZ/SZA/BPP)	---	18/9/4	---
Visual Acuity	0.88 (0.194)	0.813 (0.283)	0.386
Social Functioning Scale	152.733 (19.601)	129.414 (20.458)	<0.001 ***
BACS Composite Z Score	-0.161 (0.755)	-0.616 (0.717)	0.057
PANSS Total Score	---	53.241 (14.503)	---
PANSS Positive Symptoms Score	---	12.633 (4.522)	---
PANSS Negative Symptoms Score	---	12.933 (4.502)	---
Young Mania Rating Scale	---	7.183 (6.329)	---

Note: SD = standard deviation; HC = healthy control; SZ = schizophrenia; SZA = schizoaffective disorder; BPP = bipolar disorder; CA = Caucasian; AA = African American; OTH = other, BACS = Brief Assessment of Cognition in Schizophrenia, PANSS = Positive and Negative Syndrome Scale. Continuous data are given as mean (SD). Significant test statistics are in bold and denoted as *** P < 0.005

Retinal Microvasculature and Perfusion Results

Results between probands and healthy controls in the FAZ analysis did not survive p value correction. Prior to correction, there were borderline significant

differences between probands and controls in the superficial and deep layers of the right eye. These layers demonstrated a strong negative effect size, Cohen's $d = -0.67$ for both the superficial and deep layers of the right eye. A negative effect size was identified between groups for all measures demonstrating HC's have a greater FAZ area compared to probands (Table 2).

Table 2: Analysis of FAZ comparing Probands to Healthy Controls			
Region	P Value	Adjusted P Value	Cohen's D
Right Superficial FAZ	0.051*	0.129	-0.674
Right Deep FAZ	0.051*	0.129	-0.674
Left Superficial FAZ	0.406	0.406	-0.278
Left Deep FAZ	0.406	0.406	-0.278
Bilateral FAZ	0.219	0.359	-0.428

Note: FAZ = foveal avascular zone. Significant test statistics are in bold and denoted as * $P < 0.05$

VD, VDI, SD, and FD measures were compared between probands and HC's (Table 3). There was no significance for any of the measures analyzed. Effect sizes for all measure were low. Right eye measures demonstrated negative effect sizes, showing HC's have greater VD, VDI, SD, and FD in the right eye. For the left eye and bilateral eye measures, VDI demonstrated a small negative effect size. VD, SD, and FD in the left eye and both eyes demonstrated positive effect sizes showing probands had greater values than HC in these categories.

Results differ when compared to a study by Bannai et al. Bannai et al determined right eye retinal measures were higher in probands compared to HC for superficial and choriocapillaris VD and FD, and choriocapillaris SD in early course patients (Bannai et al., 2022). The lack of significance in results for this study is likely due to heterogeneity of the proband group and small sample size.

Table 3: Analysis of VD, VDI, SD, and FD Comparing Probands and Healthy Control		
Region	P Value	Cohen's D
Bilateral		
VD	0.962	0.015
VDI	0.812	-0.078
SD	0.872	0.053
FD	0.987	0.005
Right		
VD	0.552	-0.196
VDI	0.622	-0.162
SD	0.609	-0.168
FD	0.566	-0.189
Left		
VD	0.541	0.209
VDI	0.850	-0.064
SD	0.388	0.296
FD	0.494	0.234

Note: VD = vessel density, VDI = vessel density index, SD = skeletal density, FD = fractal dimension

Lobe-wise brain perfusion was analyzed in HC compared to probands (Figure 5) and there were no significant findings. Perfusion in the temporal, parietal, and

occipital lobes demonstrated positive effect sizes while the relationship between groups for frontal perfusion demonstrated a small negative effect size. When perfusion was analyzed based on laterality, there were no significant results and all portions analyzed demonstrated similar small positive effect sizes (Figure 6). The lack of significance between groups may be due to the heterogeneity of the sample. The proband group consisted of individuals with a diagnosis of SZ, SZA, or BPD.

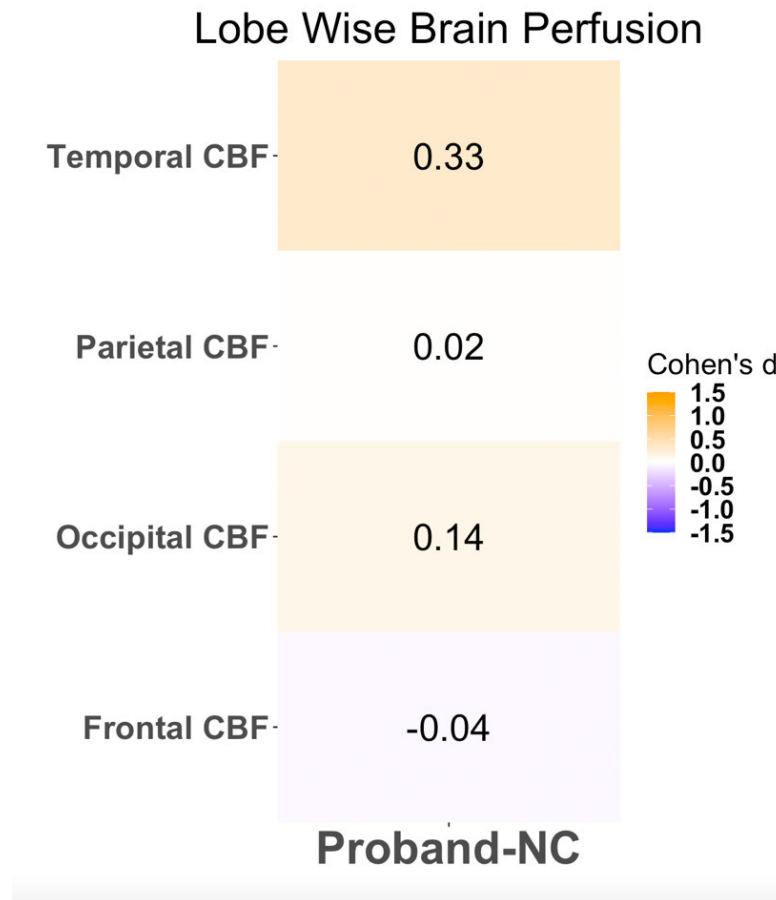


Figure 5: Bilateral lobe-wise brain perfusion comparing probands to normal controls (NC). Cohen's d estimates adjusted for age, sex, and race.

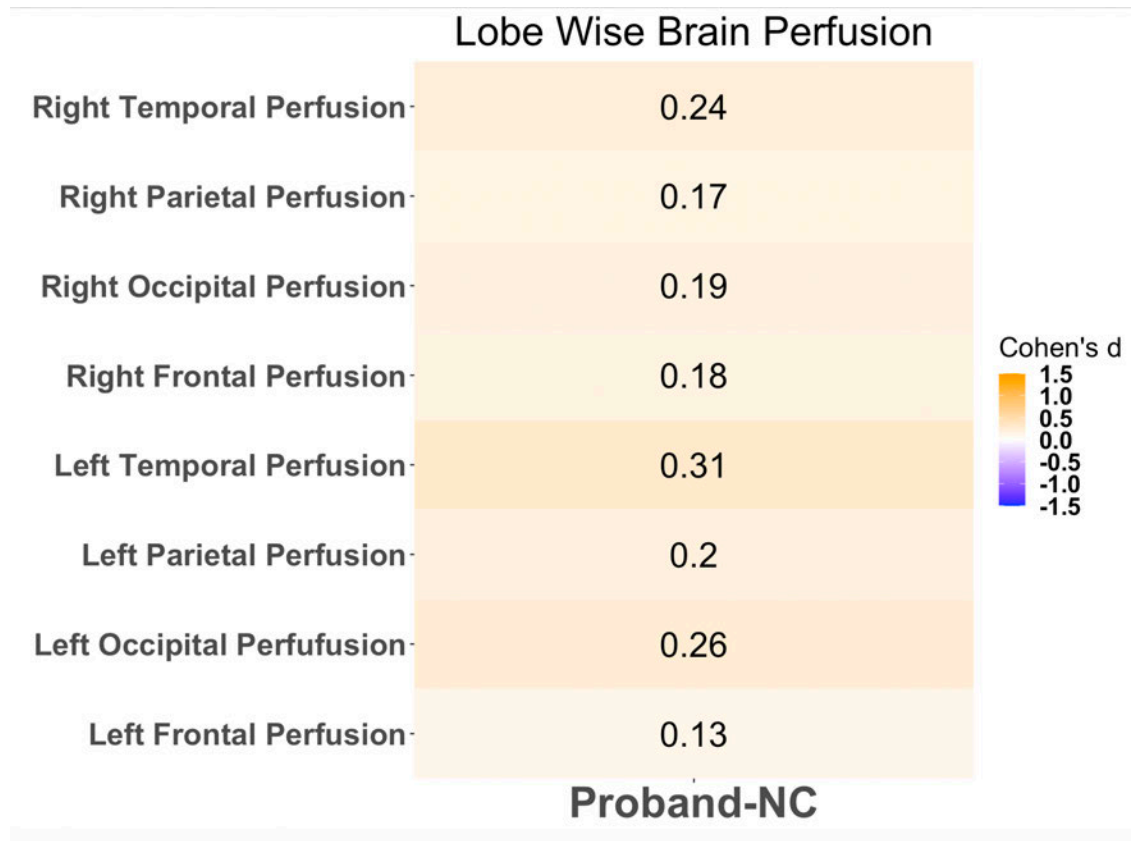


Figure 6: Lobe Wise Brain Perfusion based on laterality comparing probands and normal controls (NC). Cohen's d estimates adjusted for age, sex, and race.

Correlations between Retinal and Brain Perfusion

Correlations between bilateral retinal measures and lobe-wise brain perfusion are displayed in Table 4. SD and FD measures showed no significant relationships when correlated with brain perfusion measures and were not further analyzed. VD and frontal perfusion was significantly correlated in HCs ($r = -0.698$, $p = 0.002$, adj $p = 0.022$) and probands ($r = 0.636$, $p = <0.001$, adj $p = 0.005$), but in an orthogonal

fashion (Figure 7). In probands only, significant relations were found between VDI and frontal perfusion ($r = 0.744$, $p = <0.001$, $\text{adj } p = 0.0003$) (Figure 8) and VDI and temporal perfusion ($r = -0.543$, $p = 0.006$, $\text{adj } p = 0.024$) (Figure 9). Additional correlations for VD, VDI and FAZ did not display significance and are shown in Table 4. In healthy controls, all R values, except for FAZ area and occipital perfusion, were negative. The directionality of results in the proband groups was mixed. Most notably, VD and frontal perfusion and VDI and frontal perfusion demonstrated large positive significant associations. Correlations between VD and temporal perfusion and VDI and temporal perfusion demonstrated negative associations.

Table 4: Analysis of Correlations between Bilateral Retinal and Brain Perfusion Measures Comparing HCs to Probands						
	HC			Probands		
Correlation	R Value	P Value	Adj P Value	R Value	P Value	Adj P Value
Vessel Density						
Frontal Perfusion	-0.698	0.002***	0.022*	0.636	<0.001***	0.005***
Temporal Perfusion	-0.530	0.029*	0.089	-0.348	0.095	0.286
Parietal Perfusion	-0.381	0.239	0.316	0.106	0.621	0.853
Occipital Perfusion	-0.148	0.255	0.763	0.076	0.725	0.853
Vessel Density Index						
Frontal Perfusion	-0.528	0.219	0.088	0.744	<0.001***	0.0003***
Temporal Perfusion	-0.537	0.218	0.088	-0.543	0.006**	0.024*
Parietal Perfusion	-0.229	0.251	0.646	-0.098	0.649	0.853
Occipital Perfusion	-0.302	0.246	0.477	-0.060	0.782	0.853
FAZ						
Frontal Perfusion	-0.063	0.277	0.907	-0.028	0.898	0.898
Temporal Perfusion	-0.219	0.271	0.648	-0.310	0.151	0.361
Parietal Perfusion	-0.017	0.277	0.953	-0.175	0.426	0.730
Occipital Perfusion	0.060	0.277	0.907	-0.222	0.310	0.619

Note: FAZ = foveal avascular zone; HC = healthy controls; adj = adjusted. Significant test statistics are in bold and denoted as * P < 0.05, **P < .01, ***P < 0.005.

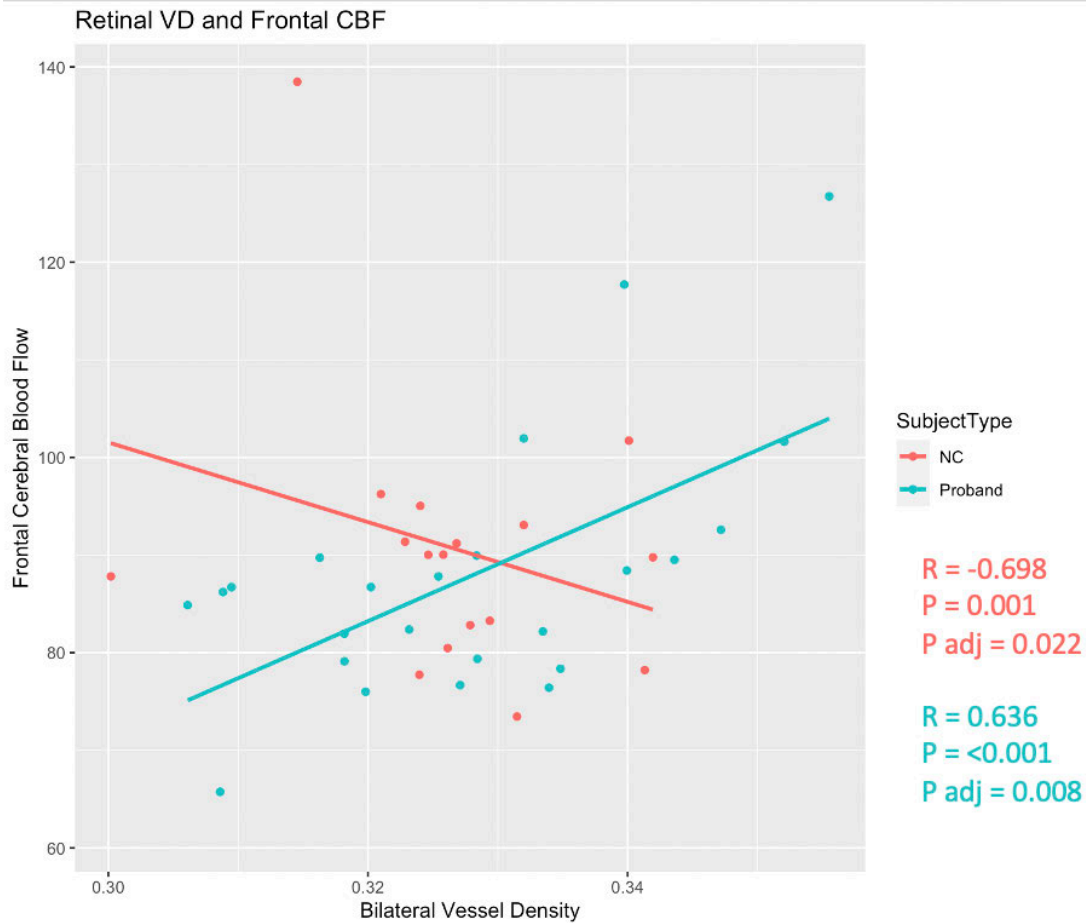


Figure 7: Bilateral retinal vessel density correlated with frontal cerebral blood flow.

Correlation of bilateral vessel density with frontal cerebral blood flow in probands compared to healthy controls. The red dots and red line are associated with normal control values and the blue dots and blue lines are associated with proband values. NC's demonstrated a negative relationship between variables and probands demonstrated a positive relationship. Note: VD = vessel density; CBF = cerebral blood flow; NC = normal control.

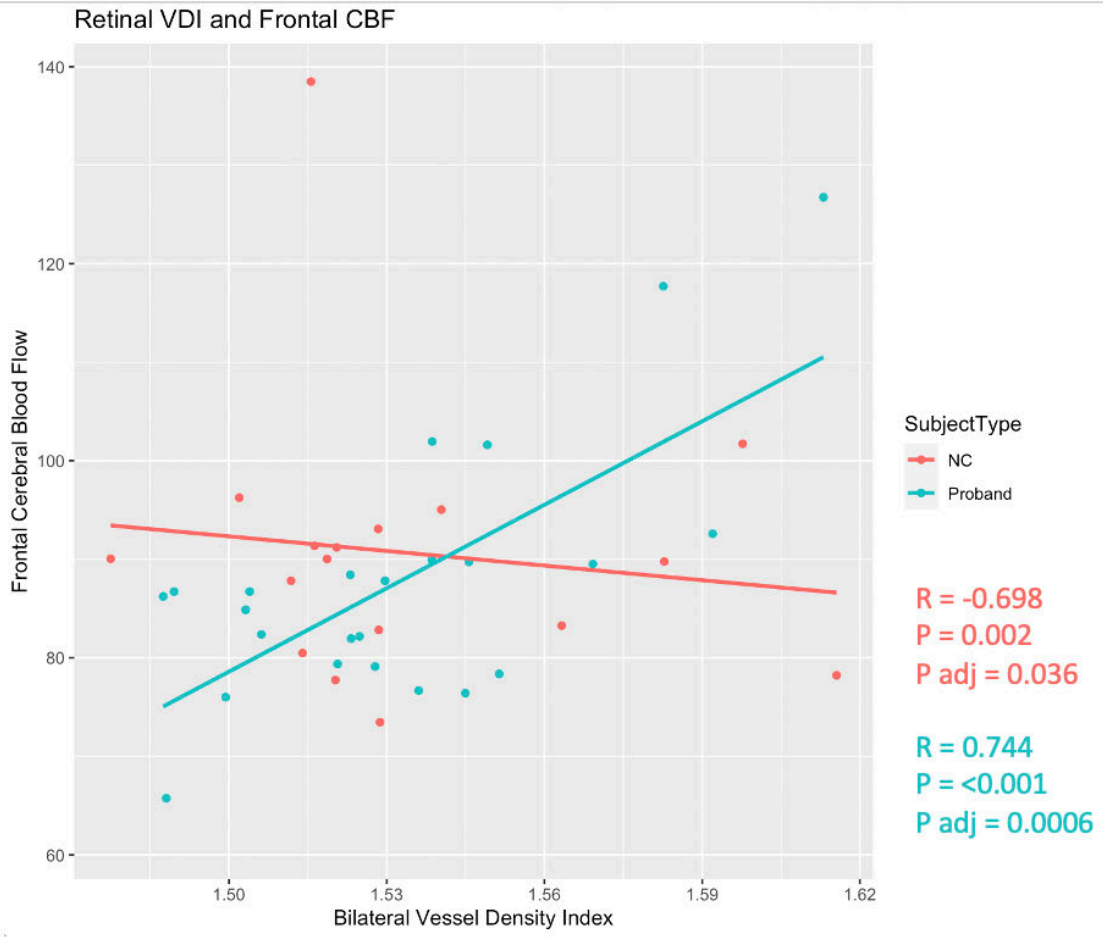


Figure 8: Bilateral retinal vessel density index correlated with frontal cerebral blood flow

Correlation of bilateral vessel density index with frontal cerebral blood flow in probands compared to healthy controls. The red dots and red line are associated with normal control values and the blue dots and blue lines are associated with proband values. NC's demonstrated a negative relationship between variables and probands

demonstrated a positive relationship. Note: VD = vessel density; CBF = cerebral blood flow; NC = normal control.

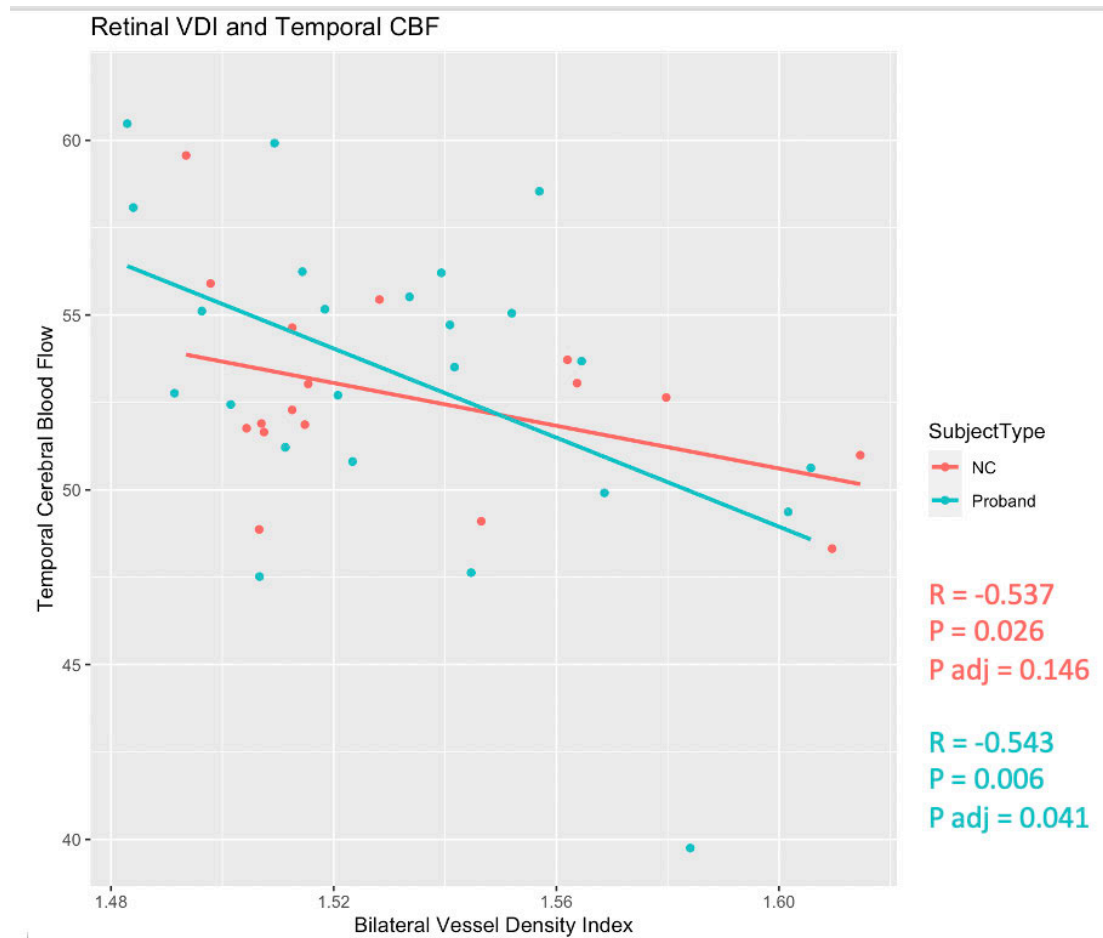


Figure 9: Bilateral retinal vessel density index correlated with temporal cerebral blood flow

Correlation of bilateral vessel density with temporal cerebral blood flow in probands compared to healthy controls. Both groups demonstrated significant negative relationships between variables with the significance in probands being greater than

NC's. The red dots and red line are associated with normal control values and the blue dots and blue lines are associated with proband values. Note: VD = vessel density; CBF = cerebral blood flow; NC = normal control.

Results that showed significance at the bilateral retinal measure level were analyzed based on individual retinal layer (Table 5). Healthy controls demonstrated significance after correction for correlations in the deep level including VDI and temporal CBF ($r = -0.624$, $\text{adj } p = 0.03$), VDI and frontal CBF ($r = -0.612$, $\text{adj } p = 0.03$), VD and frontal CBF ($r = -0.597$, $\text{adj } p = 0.03$), and VD and temporal CBF ($r = -0.573$, $\text{adj } p = 0.03$). Probands demonstrated significance for various measure across all three layers. In the superficial layer, VDI and frontal CBF ($r = 0.628$, $\text{adj } p = 0.008$), superficial VDI and temporal CBF ($r = -0.481$, $p = 0.017$, $\text{adj } p = 0.06$) and superficial VD and frontal CBF ($r = 0.46$, $p = 0.024$, $\text{adj } p = 0.063$) were significant prior to p value adjustment. R values for the temporal (VD: $r = -0.172$, $p = 0.420$; VDI: $r = -0.481$, $p = 0.017$), parietal (VD: $r = -0.038$, $p = 0.858$; VDI: $r = -0.191$, $p = 0.371$), and occipital lobe (VD: $r = -0.224$, $p = 0.293$; VDI: $r = -0.162$, $p = 0.448$) in the superficial layer were negative while frontal perfusion correlation R values (VD: $r = 0.460$, $p = 0.024$; VDI: $r = 0.628$, $p = 0.001$) were positive for the proband group. In the deep layer, VDI and VD each correlated with frontal CBF and were significant with positive R values ($r = 0.752$, $\text{adj } p = 0.0002$) and ($r = 0.627$, $\text{adj } p = 0.004$) respectively. R values for additional deep layer correlations in the parietal (VD: $r = 0.229$, $p = 0.281$; VDI: $r =$

0.135, $p = 0.529$) and occipital lobes (VD: $r = 0.096$, $p = 0.656$; VDI: $r = 0.063$, $p = 0.771$) demonstrated positive relationships whereas the temporal lobe correlations with VD ($r = -0.350$, $p = 0.094$) and VDI ($r = -0.47$, $p = 0.02$) demonstrated negative relationships. In the choriocapillaris layer, VDI and parietal CBF ($r = -0.466$, $p = 0.022$) and VD and occipital CBF ($r = 0.458$, $p = 0.024$) were significant prior to p value correction.

Table 5: Analysis of Correlations between Retinal and Brain Perfusion Measures Comparing HCs to Probands Based on Retinal Layer for Bilateral Measures							
Layer		HC			Probands		
		R	P	Adj P	R	P	Adj P
Sup	VD and Frontal Perfusion	-0.299	0.244	0.488	0.46	0.024**	0.063
	VD and Temporal Perfusion	-0.002	0.993	0.993	-0.172	0.420	0.511
	VD and Parietal Perfusion	-0.043	0.871	0.993	-0.038	0.858	0.858
	VD and Occipital Perfusion	-0.252	0.328	0.526	-0.224	0.293	0.511
	VDI and Frontal Perfusion	-0.404	0.108	0.326	0.628	0.001** *	0.008** *
	VDI and Temporal Perfusion	-0.390	0.122	0.326	-0.481	0.017**	0.060
	VDI and Parietal Perfusion	-0.062	0.812	0.994	-0.191	0.371	0.511

	VDI and Occipital Perfusion	-0.390	0.122	0.326	-0.162	0.448	0.0511
Deep	VD and Frontal Perfusion	-0.597	0.011*	0.03*	0.627	0.001**	0.004**
	VD and Temporal Perfusion	-0.573	0.016*	0.032*	-0.350	0.094	0.188
	VD and Parietal Perfusion	-0.368	0.147	0.196	0.229	0.281	0.450
	VD and Occipital Perfusion	0.014	0.957	0.957	0.096	0.656	0.750
	VDI and Frontal Perfusion	-0.612	0.009*	0.030*	0.752	<0.001	0.0002
	VDI and Temporal Perfusion	-0.624	0.007*	0.030*	-0.470	0.02**	0.054*
	VDI and Parietal Perfusion	-0.369	0.145	0.196	0.135	0.529	0.704
	VDI and Occipital Perfusion	-0.122	0.639	0.731	0.063	0.771	0.771
Cho	VD and Frontal Perfusion	-0.176	0.499	0.598	-0.08	0.709	0.811
	VD and Temporal Perfusion	-0.166	0.523	0.598	-0.088	0.682	0.811
	VD and Parietal Perfusion	-0.181	0.486	0.598	-0.245	0.248	0.397
	VD and Occipital Perfusion	-0.124	0.632	0.633	0.458	0.024*	0.098
	VDI and Frontal Perfusion	-0.288	0.262	0.598	0.291	0.168	0.335

	VDI and Temporal Perfusion	-0.355	0.162	0.598	-0.417	0.043*	0.114
	VDI and Parietal Perfusion	-0.199	0.444	0.598	-0.466	0.022*	0.098
	VDI and Occipital Perfusion	-0.277	0.281	0.598	-0.008	0.970	0.970

Note: Sup = Superficial; Cho = Choriocapillaris, VD = Vessel Density, VDI = Vessel Density Index, HC = healthy control; Adj = adjusted. Significant test statistics are in bold and denoted as *P < 0.05, **P < 0.01, ***P < 0.005.

To determine if the right or left eye was driving significance in bilateral analysis, measures were analyzed based on laterality. Results for the right eye are displayed in Table 6 and the left eye in Table 7. Left eye VDI measures were the driving factor for significance in healthy controls. Left eye superficial VDI and frontal CBF demonstrated significance ($r = -0.709$, $p = 0.003$, $\text{adj } p = 0.019$). No additional measures were of note in HCs based on laterality. The deep and choriocapillaris layers of the left eye were the driving forces for proband significance in the VD correlations with deep VD and frontal lobe CBF having greater significance and strength ($r = 0.607$, $p = 0.001$, $\text{adj } p = 0.020$) compared to choriocapillaris layer VD and temporal CBF ($r = -0.502$, $p = 0.012$, $\text{adj } p = 0.050$). VDI analysis of layers based on right and left eye had numerous significant findings. For VDI relationship to frontal perfusion, both eyes are contributing to bilateral significance. In the right eye, deep VDI and frontal perfusion ($r = 0.689$, $p = 0.0002$, $\text{adj } p = 0.002$) as well as superficial VDI and frontal

perfusion ($r = 0.660$, $p = 0.0004$, $\text{adj } p = 0.003$) demonstrated significance with great strength. The left eye demonstrated significance in deep VDI and frontal perfusion ($r = 0.694$, $p = 0.0002$, $\text{adj } p = 0.002$) as well as the superficial VDI and frontal perfusion ($r = 0.514$, $p = 0.010$, $\text{adj } p = 0.041$) correlation. The effect size in the left eye superficial VDI and frontal perfusion is slightly less than the right eye. Bilateral temporal perfusion significance is driven largely by right eye measures. Right eye findings include superficial VDI and temporal perfusion ($r = -0.576$, $p = 0.003$, $\text{adj } p = 0.013$) and deep VDI and temporal perfusion ($r = -0.459$, $p = 0.024$, $\text{adj } p = 0.072$). Left eye demonstrated significance in choriocapillaris VDI and temporal perfusion ($r = -0.598$, $p = 0.002$, $\text{adj } p = 0.012$). Parietal and occipital lobe correlations did not display significance or large effect sizes in relationships. Results demonstrate retinal perfusion may be a proxy for frontal lobe perfusion.

Table 6: Analysis of Correlations between Retinal and Brain Perfusion Measures Comparing HCs to Probands Based on Retinal Layer for Right Eye Measures

Layer	Lobe	HC			Probands		
		R	P	Adj P	R	P	Adj P
Sup VDI	Frontal	-0.442	0.075	0.226	0.66	<0.001***	0.003***
	Temporal	-0.56	0.019*	0.111	-0.576	0.003***	0.013*
	Parietal	-0.115	0.659	0.719	-0.147	0.492	0.702
Deep VDI	Occipital	-0.303	0.237	0.355	-0.178	0.405	0.700
	Frontal	-0.483	0.050*	0.198	0.689	<0.001***	0.002***
	Temporal	-0.578	0.015*	0.111	-0.459	0.023*	0.071
Cho VDI	Parietal	-0.348	0.171	0.305	0.201	0.345	0.690
	Occipital	0.016	0.950	0.950	0.122	0.569	0.702
	Frontal	-0.343	0.178	0.305	0.026	0.904	0.957
Sup VD	Temporal	-0.365	0.150	0.305	0.117	0.584	0.702
	Parietal	-0.275	0.285	0.380	-0.224	0.292	0.690
	Occipital	-0.222	0.391	0.470	-0.011	0.957	0.957
Deep VD	Frontal	-0.579	0.014*	0.178	0.402	0.051	0.254
	Temporal	0.031	0.907	0.907	-0.199	0.351	0.469
	Parietal	-0.213	0.411	0.663	0.011	0.959	0.959
Cho VD	Occipital	-0.407	0.104	0.399	-0.203	0.340	0.469
	Frontal	-0.453	0.068	0.399	0.479	0.017*	0.213
	Temporal	-0.332	0.192	0.460	-0.301	0.152	0.330
Deep VD	Parietal	-0.380	0.133	0.399	0.276	0.192	0.330
	Occipital	0.146	0.577	0.761	0.125	0.562	0.612
	Frontal	-0.199	0.442	0.663	-0.278	0.188	0.330
Cho VD	Temporal	-0.083	0.752	0.820	0.384	0.063	0.255
	Parietal	-0.213	0.410	0.663	0.167	0.435	0.522
	Occipital	-0.125	0.633	0.761	0.347	0.100	0.300

Note: Sup = Superficial; Cho = Choriocapillaris, VD = Vessel Density, VDI = Vessel Density Index, HC = healthy control; Adj = adjusted. Significant test statistics are in bold and denoted as *P < 0.05, **P < 0.01, ***P < 0.005.

Table 7: Table 2: Analysis of Correlations between Retinal and Brain Perfusion Measures Comparing HCs to Probands Based on Retinal Layer for Left Eye Measures							
Layer	Lobe	HC			Probands		
		R	P	Adj P	R	P	Adj P
Sup VDI	Frontal	-0.624	0.013*	0.052	0.514	0.010**	0.041*
	Temporal	0.111	0.692	0.692	-0.333	0.111	0.191
	Parietal	-0.370	0.175	0.263	-0.203	0.342	0.513
Deep VDI	Occipital	-0.734	0.002***	0.019*	-0.127	0.554	0.739
	Frontal	-0.709	0.003***	0.019*	0.694	<0.001***	0.002***
	Temporal	0.575	0.025*	0.06	-0.413	0.045*	0.107
Cho VDI	Parietal	-0.486	0.066	0.121	0.068	0.753	0.903
	Occipital	-0.258	0.352	0.422	0.010	0.962	0.989
	Frontal	-0.479	0.071	0.121	0.349	0.095	0.189
Sup VD	Temporal	-0.204	0.466	0.508	-0.598	0.002***	0.012***
	Parietal	-0.279	0.314	0.420	-0.444	0.030*	0.090
	Occipital	-0.574	0.025*	0.060	-0.003	0.989	0.989
Deep VD	Frontal	0.020	0.942	0.942	0.361	0.083	0.250
	Temporal	0.132	0.636	0.924	-0.074	0.732	0.799
	Parietal	-0.032	0.909	0.942	-0.087	0.685	0.799
Sup VDI	Occipital	-0.820	0.770	0.924	-0.166	0.439	0.659
	Frontal	-0.554	0.032*	0.192	0.608	0.002***	0.02*
	Temporal	-0.603	0.017*	0.192	-0.312	0.138	0.330
Deep VDI	Parietal	-0.344	0.209	0.742	0.141	0.510	0.681
	Occipital	-0.098	0.729	0.924	0.051	0.811	0.811

Cho VD	Frontal	-0.286	0.301	0.742	0.166	0.437	0.659
	Temporal	-0.113	0.687	0.924	-0.502	0.012*	0.05*
	Parietal	-0.141	0.616	0.924	-0.502	0.012*	0.05*
	Occipital	-0.281	0.309	0.742	0.285	0.176	0.353

Note: Sup = Superficial; Cho = Choriocapillaris, VD = Vessel Density, VDI = Vessel Density Index, HC = healthy control; Adj = adjusted. Significant test statistics are in bold and denoted as *P < 0.05, **P < 0.01, ***P < 0.005.

Retinal and Brain Perfusion Correlations with Clinical Measures

Retinal measures were correlated with clinical measures including PANSS, YMRS, BACS, and Birchwood SFS to determine if perfusion rates influenced scores on the assessments. Probands have data for all four scales. Healthy controls were only assessed utilizing BACS and the Birchwood SFS scales.

PANSS total scores were significantly correlated with bilateral SD ($r = 0.525$, $p = 0.012$, adj $p = 0.040$) (Figure 10) and bilateral FD ($r = 0.508$, $p = 0.016$, adj $p = 0.040$) (Figure 11). When analyzing total positive scores on PANSS, there was no significance with retinal measures. Correlations of retinal measures with total negative PANSS scores demonstrated significance in bilateral SD ($r = 0.516$, $p = 0.012$, adj $p = 0.028$), bilateral FD ($r = 0.510$, $p = 0.013$, adj $p = 0.028$), bilateral VD ($r = 0.474$, $p = 0.022$, adj $p = 0.028$) and FAZ area ($r = 0.194$, $p = 0.018$, adj $p = 0.028$). There was no significance between PANSS total, positive, or negative scores and VDI. Lobe-wise brain perfusion demonstrated no significance when correlated with total PANSS score, positive PANSS score, or negative PANSS score.

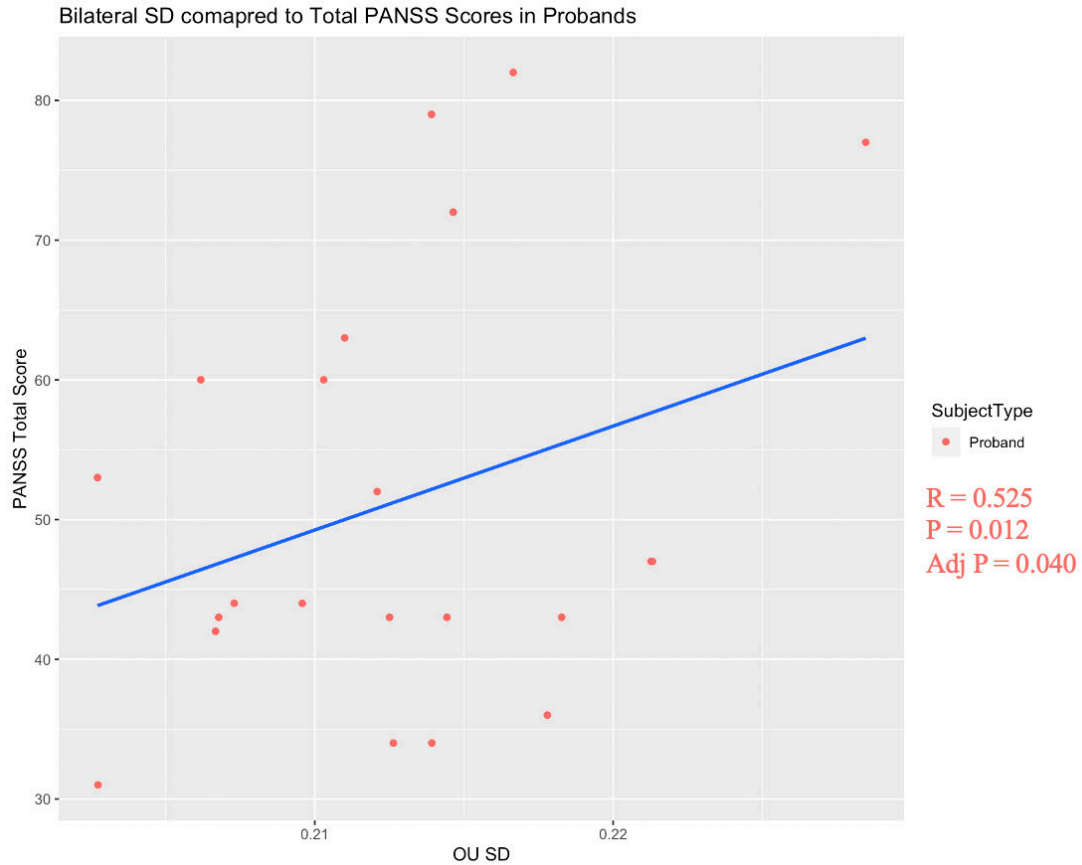


Figure 10: Bilateral Skeletal Density compared to Total PANSS Scores in Probands

Correlation of bilateral skeletal density with total PANSS score in probands. PANSS score was significantly positively correlated with bilateral SD. The red points represent the score of individual subjects, and the blue line represents the trend for the proband group. Note: SD = skeletal density; PANSS = Positive and Negative Syndrome Scale; Adj = adjusted.

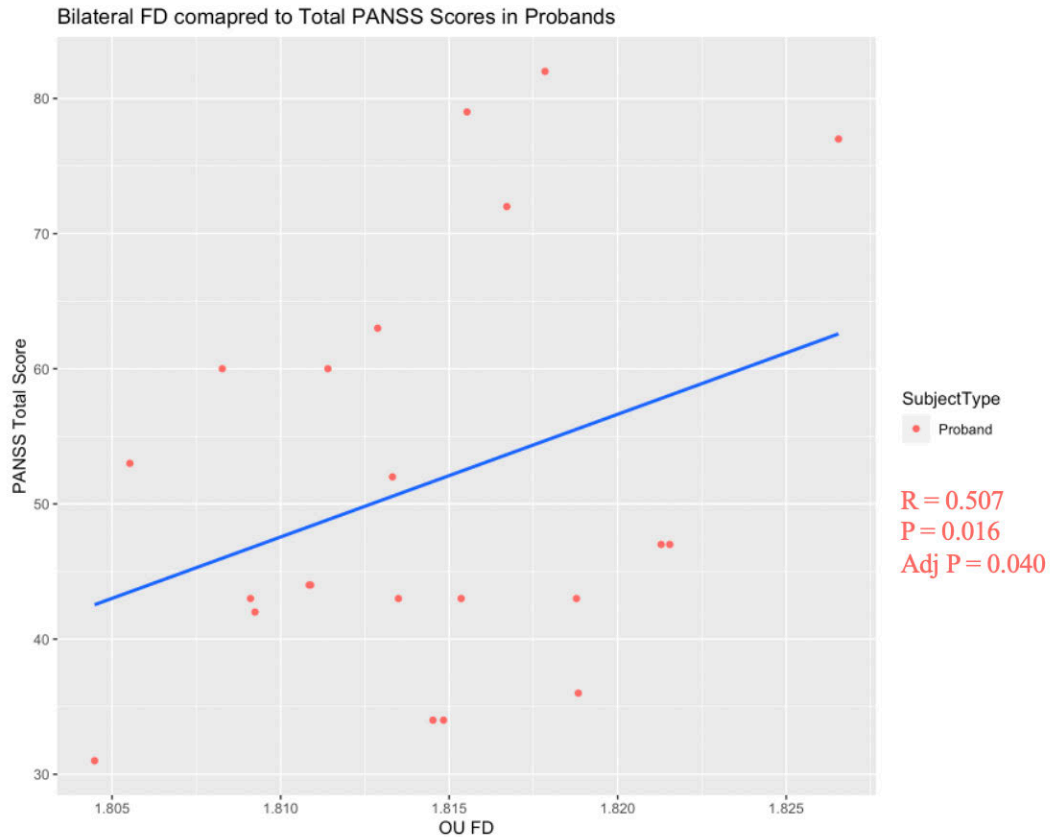


Figure 11: Bilateral FD compared to Total PANSS Scores in Probands

Correlation of bilateral fractal density with total PANSS score in probands. PANSS score was significantly positively correlated with bilateral FD. Strength of association between variables is strong based on $r = 0.507$. The red points represent individual subjects, and the blue line represents the trend for the proband group. Note: FD = fractal dimension; PANSS = Positive and Negative Syndrome Scale; Adj = adjusted.

YMRS and bilateral FAZ area showed significance prior to P value correction ($r = -0.496$, $p = 0.019$, $adj\ p = 0.094$). Correlations of retinal measures VD, VDI, SD, and

FD with YMRS scores showed no significance. When YMRS was compared to brain perfusion measure for the frontal, temporal, parietal, and occipital lobes there was no significance. The relationship between lobes analyzed and YMRS was positive for all cases analyzed showing perfusion increases with YMRS scores.

The BACS assessment was performed in proband and healthy control groups (Table 8). The six BACS assessments including: verbal memory, digit sequencing, token motor, verbal fluency, symbol coding, and tower of London tasks, along with composite score were correlated with retinal and brain perfusion measures. Significance was demonstrated in retinal correlations. In probands, significance was found in the following correlations prior to p value adjustment: bilateral FAZ area and token motor task ($r = 0.542$, $p = 0.011$, $\text{adj } p = 0.056$), bilateral FD and tower of London ($r = 0.441$, $p = 0.040$, $\text{adj } p = 0.104$) and bilateral SD and tower of London ($r = 0.437$, $p = 0.042$, $\text{adj } p = 0.104$). Healthy controls demonstrated significance in bilateral FAZ and verbal fluency ($r = 0.622$, $p = 0.017$, $\text{adj } p = 0.087$), bilateral VD and tower of London ($r = 0.605$, $p = 0.017$, $\text{adj } p = 0.084$) and bilateral VDI and tower of London ($r = 0.541$, $p = 0.038$, $\text{adj } p = 0.094$). Significance in healthy controls does not survive p value correction. When analyzing BACS scores for each of the six tasks and the composite score, there was no significance when correlated with lobe-wise brain perfusion in probands or healthy controls.

Table 8: Analysis of Correlations between Bilateral Retinal Perfusion Measures and BACS scores in Probands and HCs

BACS Measure	Retinal Measure	HC			Probands		
		R	P	Adj P	R	P	Adj P
Verbal Memory	VD	0.242	0.366	0.787	0.199	0.373	0.559
	VDI	0.168	0.531	0.787	0.168	0.454	0.559
	SD	0.142	0.599	0.787	0.173	0.441	0.559
	FD	0.092	0.736	0.787	0.183	0.415	0.559
	FAZ	0.080	0.786	0.787	0.135	0.559	0.559
Digit Sequencing	VD	0.153	0.572	0.814	0.036	0.873	0.997
	VDI	-0.112	0.677	0.814	0.026	0.907	0.997
	SD	0.304	0.251	0.814	0.015	0.947	0.997
	FD	0.257	0.337	0.814	<0.001	0.997	0.997
	FAZ	-0.070	0.814	0.814	-0.208	0.947	0.997
Token Motor	VD	-0.183	0.497	0.753	0.019	0.934	0.934
	VDI	-0.091	0.738	0.753	-0.157	0.482	0.622
	SD	-0.133	0.622	0.753	0.153	0.497	0.622
	FD	-0.145	0.591	0.753	0.172	0.443	0.622
	FAZ	0.092	0.753	0.753	0.542	0.011*	0.6222
Verbal Fluency	VD	0.159	0.555	0.694	-0.079	0.727	0.888
	VDI	-0.107	0.694	0.694	-0.073	0.744	0.888
	SD	0.393	0.132	0.291	-0.089	0.694	0.888
	FD	0.357	0.175	0.291	-0.094	0.677	0.888
	FAZ	0.622	0.017*	0.087	-0.033	0.888	0.888
Sequence Coding	VD	0.192	0.475	0.965	0.161	0.474	0.646
	VDI	0.260	0.330	0.965	0.130	0.563	0.646
	SD	-0.012	0.965	0.965	0.129	0.566	0.646
	FD	-0.057	0.833	0.965	0.135	0.549	0.646
	FAZ	0.073	0.803	0.965	-0.106	0.645	0.646
Tower of London	VD	0.605	0.017*	0.084	0.387	0.076	0.125
	VDI	0.540	0.037*	0.093	0.225	0.313	0.343
	SD	0.255	0.359	0.599	0.437	0.042*	0.104
	FD	0.180	0.521	0.651	0.441	0.039*	0.104

	FAZ	0.132	0.667	0.667	0.217	0.343	0.343
Composite Score	VD	0.204	0.464	0.773	0.298	0.178	0.297
	VDI	0.284	0.304	0.761	0.155	0.492	0.492
	SD	-0.059	0.835	0.835	0.333	0.129	0.297
	FD	-0.099	0.724	0.835	0.335	0.127	0.297
	FAZ	0.531	0.062	0.308	0.255	0.264	0.33

Note: BACS = Brief Assessment of Cognition; VD = vessel density; VDI = vessel density index; FD = fractal dimension; SD = skeletal density; FAZ = foveal avascular zone; HC = healthy control; Adj = adjusted. Significant test statistics are in bold and denoted as *P <0.05.

Birchwood SFS showed no significant relationship with retinal or brain perfusion measures in healthy controls or proband groups. The relationship between retinal perfusion measures and SFS total score was negative for all groups including: FAZ area, bilateral VD, bilateral VDI, bilateral SD, and bilateral FD. The relationship between lobe-wise brain perfusion and SFS total score was negative for the frontal, occipital, and parietal lobes. SFS and temporal lobe perfusion demonstrated a positive relationship in HC's and probands.

Discussion

Brain Perfusion and Retinal Perfusion in Psychosis

In this study, we found retinal perfusion and brain perfusion to have no significant differences in probands compared to healthy controls when measures were analyzed individually. This result is different from other studies conducted.

Bannai et al determined significance in the right eye for superficial SD, choriocapillaris VD, and choriocapillaris SD demonstrating probands to have greater SD and VD compared to controls (Bannai et al., 2022). The lack of significance between proband and healthy control retinal measures in this study is likely due to the heterogeneity of the sample. Bannai et al included 8 early course and 15 chronic individuals in the proband group. The early course SZ individuals demonstrated higher values for superficial and choriocapillaris VD and FD, and choriocapillaris SD in early course patients and individuals in the chronic phase had no significant differences when compared to HCs (Bannai et al., 2022). Silverstein et al identified probands to have a reduction in perfusion density and VD in the left eye and a reduction in perfusion density in the right eye. Silverstein et al report significant enlargement of FAZ bilaterally in probands compared to HCs (Silverstein et al., 2021). The lack of consistent results across studies suggests retinal perfusion in probands is altered but the directionality is unclear. Research in AD demonstrates similar retinal structural changes to psychosis. A review of 71 studies on retinal changes in AD reported reduced VD and perfusion density in the superficial and deep layers and an enhanced FAZ area (Song et al., 2021) which are similar to the results demonstrated by Silverstein et al when analyzing psychosis.

A meta-analysis on brain perfusion changes in schizophrenia (HC n = 584, SZ n = 557) identified lower perfusion rates in the frontoinsular cortex, bilateral dorsal anterior cingulate cortex and increased perfusion rates in the bilateral dorsum

striatum and temporal pole (Sukumar et al., 2020). Our study had a significantly smaller sample size and the heterogeneity of the proband group is likely to be affecting the results. Sukumar et al only included individuals with a SZ whereas our proband group includes individuals with a SZ, SZA, or BPD diagnosis. Early course and chronic SZ patients were included in Sukumar et al meta-analysis (Sukumar et al., 2020). Our study only includes early course patients and there is potential chronic phase patients have greater differences compared to healthy controls and are contributing more to the significance of results in other studies.

Relationship between Brain Perfusion and Retinal Perfusion in Psychosis

To our knowledge, this is the first psychosis study to correlate retinal and brain perfusion. We identified frontal lobe perfusion to be positively associated with VD ($r = 0.636$, $p = <0.001$, $\text{adj } p = 0.005$) and VDI ($r = 0.744$, $p = <0.001$, $\text{adj } p = 0.0003$) in proband groups. When correlating VD with frontal perfusion in HC ($r = -0.698$, $p = 0.002$, $\text{adj } p = 0.022$) the relationship is negative and in probands ($r = 0.636$, $p = <0.001$, $\text{adj } p = 0.005$) the relationship is positive. This difference a unique relationship in probands compared to HC and agrees with our hypothesis. The frontal lobe perfusion relationship to VD can potentially be used to predict frontal perfusion changes based on retinal perfusion in probands. The relationship between temporal lobe perfusion and VD and VDI was negative for healthy control and proband groups. This positive relationship between frontal lobe perfusion and VD and VDI and negative

relationship between temporal lobe perfusion and VD and VDI remained consistent across numerous correlations including analysis of retinal perfusion based on layer (superficial, deep, choriocapillaris) with brain perfusion and retinal perfusion based on layer and laterization. No significant relationships were identified when analyzing brain perfusion with SD or FD retinal measures. The relationship between brain and retinal perfusion has been analyzed in AD and patients with an AD diagnosis were identified to have decreased VD and reduced cerebral blood flow (Berisha et al., 2007; Lahme et al., 2018). Retinal structure and perfusion change in AD are similar to those seen in this study in psychosis. The relationship between retinal perfusion and brain perfusion should be further analyzed to determine if retinal perfusion can be utilized to predict brain perfusion changes.

Relationship Brain Perfusion and Retinal Perfusion to Clinical Measures

Clinical scale measures were analyzed in relation to retinal and brain perfusion measures. PANSS and YMRS were only analyzed in the proband group. Total, positive and negative PANSS scores and lobe-wise brain perfusion showed no significance. Total PANSS scores and retinal perfusion showed significance for some measures including bilateral SD ($r = 0.525$, $p = 0.012$, $\text{adj } p = 0.040$) and bilateral FD ($r = 0.508$, $p = 0.016$, $\text{adj } p = 0.040$). These results are interesting given that SD and FD measures showed no significance when analyzing retinal perfusion in probands and healthy controls as well as when correlating retinal and brain perfusion. Results

differ from current literature demonstrating a relationship between higher PANSS scores and greater superficial VS and deep VDI in chronic populations (Bannai et al., 2022). Our study analyzed early course patients which may be the reason for the different results. When correlating negative PANSS scores with bilateral retinal measures, there was a positive significant relationship with bilateral SD ($r = 0.516$, $p = 0.012$, $\text{adj } p = 0.028$) and bilateral FD ($r = 0.510$, $p = 0.013$, $\text{adj } p = 0.028$), bilateral VD ($r = 0.474$, $p = 0.022$, $\text{adj } p = 0.028$) and FAZ area ($r = 0.194$, $p = 0.018$, $\text{adj } p = 0.028$) demonstrating PANSS scores increase with increased retinal perfusion. This findings goes against our hypothesis that probands with increased symptoms would demonstrate decreased perfusion. Additional studies are needed to analyze the relationship between PANSS scores and retinal perfusion measures in early course compared to chronic phase patients along with the impact medication has on managing symptoms and the corresponding relationship to PANSS score changes.

When analyzing the extent of mania symptoms based on YMRS and perfusion rates in the retina and brain there was no significant results. Despite nonsignificant results across all lobe-wise brain perfusion measures, there was a positive relationship between variables. The relationship between YMRS and FAZ area, bilateral VDI, and bilateral VD was negative while the relationship between bilateral FD and bilateral SD with YMRS was positive. Interestingly, the relationship between FD and SD to YMRS was different from other comparative measures and when

analyzing FD and SD to additional clinical scales, such as PANSS, significance was identified.

BACS and the Birchwood SFS were analyzed in probands and healthy controls. A prior study identified healthy controls to performed better then probands in all six tasks (R. S. E. Keefe et al., 2004). We aimed to determine if BACS differences between healthy controls and probands was related to retinal or brain perfusion. No significance was found when correlating lobe-wise brain perfusion with BACS composite score or with scores for each of the assessments. In probands, there was significance between numerous retinal perfusion measures and BACS assessments including: bilateral FAZ area and token motor task ($r = 0.542$, $p = 0.011$, adj $p = 0.056$), bilateral FD and tower of London ($r = 0.441$, $p = 0.040$, adj $p = 0.104$) and bilateral SD and tower of London ($r = 0.437$, $p = 0.042$, adj $p = 0.104$). Healthy controls demonstrated significance when comparing with retinal perfusion measures in the following tasks: bilateral FAZ and verbal fluency ($r = 0.622$, $p = 0.017$, adj $p = 0.087$), bilateral VD and tower of London ($r = 0.605$, $p = 0.017$, adj $p = 0.084$) and bilateral VDI and tower of London ($r = 0.541$, $p = 0.038$, adj $p = 0.094$). Both groups demonstrated a positive significant relationship between various retinal measures and the tower of London task suggesting a possible relationship. Bannai et al identified an association between better BACS scores and lower deep VD, deep SD, and deep FD in HCs and smaller deep VD, deep SD, and deep FD related to lower BACS scores in probands (Bannai et al., 2022). Our study only analyzed BACS scores to

bilateral VD, VDI, SD, and FD including the superficial, deep, and choriocapillaris layers in one measurement limiting our ability to attribute significant results to a certain retinal layer. The relationship between BACS composite score and VD, VDI, and FAZ measures were positive in HCs and probands. Results for comparisons of BACS composite score with SD and FD demonstrate negative relationship in HCs and a positive relationship in probands, similar to Bannai et al (Bannai et al., 2022). When correlating bilateral FAZ area with the token motor assessment in probands, there was a strong positive association. When correlating bilateral FAZ area with verbal fluency in healthy controls, there was a strong positive association. The difference in relationship identified with FAZ area and BACS tasks suggests a possible relationship between the measures that is unique in probands. The FAZ area between probands and healthy controls was not determined to be of significance, a finding that Bannai et al have determined as well (Bannai et al., 2022). These results have significant implications for future studies to further analyze the connection between BACS sub and composite scores and retinal perfusion measures. These results suggest retinal microvasculr measures have potential to monitor symptom severity and cognition in psychosis disorders. Future studies should expand the analysis between BACS scores and retinal perfusion to determine if the significance is largely from a particular eye and/or region as well as comparing early course and chronic patients. Another important question is if the relationship between retinal perfusion measures and BACS changes with treatment.

When correlating Birchwood SFS with retinal perfusion measures, we identified a negative relationship between SFS score and retinal perfusion measures (FAZ, VD, VDI, SD, FD) and between SFS scores and lobe-wise brain perfusion in the frontal, parietal, and occipital lobes in both groups. When correlating Birchwood SFS with temporal perfusion in probands and healthy controls, there was a nonsignificant positive relationship showing SFS scores increase with temporal perfusion. Higher scores on the SFS assessment are associated with more competent behavior or higher frequency of the behavior (Birchwood et al., 1990). There was a significant difference between SFS scores between groups ($p < 0.001$) demonstrating healthy controls have more competent social behavior compared to probands. Bannai et al analyzed the relationship between SFS and retinal perfusion and identified no significant relationships as well (Bannai et al., 2022). Given this, the SFS scores may be not be a good predictor of retinal perfusion changes in psychosis patients.

Conclusion

The study has several strengths as well as limitations. The study was limited by the relatively small sample size ($n = 48$, HC $n = 17$, proband $n = 31$). Despite this, retinal perfusion may serve as a biomarker for frontal and temporal brain perfusion and symptom severity based on PANSS. Studies have analyzed the differences in BACS scores in probands and healthy controls and here we aim to connect cognition scales with perfusion rates in the retina and brain (R. S. E. Keefe et al., 2004). The various

results identified between retinal perfusion and BACS tasks suggests future literature should further analyze this relationship to determine if BACS scores can predict retinal perfusion changes in psychosis. With current literature being small and demonstrating varied results, additional studies with larger samples sizes are necessary to fully determine the retinal and brain relationship in perfusion. The findings of this study add the connection between brain and retinal perfusion to literature and the effects perfusion has on clinical scales. Future work should analyze stage-specific alterations in probands to determine how retinal pathologies and perfusion alterations change with disease progression to add to the growing interest of utilizing retinal pathophysiology as a mechanism to detect neuropsychiatric disorder.

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CURRICULUM VITAE

